AROMATIC SULFONE HYDROXAMATES AND THEIR USE AS PROTEASE INHIBITORS

PRIORITY CLAIM TO RELATED PATENT APPLICATION

[1] This patent claims priority to U.S. Provisional Patent Application Serial No. 60/290,375 (filed May 11, 2001). The entire text of U.S. Provisional Patent Application Serial No. 60/290,375 is incorporated by reference into this patent.

FIELD OF THE INVENTION

[2] This invention is directed generally to proteinase (also known as "protease") inhibitors, and, more particularly, to aromatic sulfone hydroxamates (also known as "aromatic sulfone hydroxamic acids") that, *inter alia,* inhibit matrix metalloproteinase (also known as "matrix metalloprotease" or "MMP") activity and/or aggrecanase activity. This invention also is directed to compositions of such inhibitors, intermediates for the syntheses of such inhibitors, methods for making such inhibitors, and methods for preventing or treating conditions associated with MMP activity and/or aggrecanase activity, particularly pathological conditions.

BACKGROUND OF THE INVENTION

[3] Connective tissue is a required component of all mammals. It provides rigidity, differentiation, attachments, and, in some cases, elasticity. Connective tissue components include, for example, collagen, elastin, proteoglycans, fibronectin, and laminin. These biochemicals make up (or are components of) structures, such as skin, bone, teeth, tendon, cartilage, basement membrane, blood vessels, cornea, and vitreous humor.

[4] Under normal conditions, connective tissue turnover and/or repair processes are in equilibrium with connective tissue production. Degradation of connective tissue is carried out by the action of proteinases released from resident tissue cells and/or invading inflammatory or tumor cells.

[5] Matrix metalloproteinases, a family of zinc-dependent proteinases, make up a major class of enzymes involved in degrading connective tissue. Matrix

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metalloproteinases are divided into classes, with some members having several different names in common use. Examples are: MMP-1 (also known as collagenase 1, fibroblast collagenase, or EC 3.4.24.3); MMP-2 (also known as gelatinase A, 72kDa gelatinase, basement membrane collagenase, or EC 3.4.24.24), MMP-3 (also known as stromelysin 1 or EC 3.4.24.17), proteoglycanase, MMP-7 (also known as matrilysin), MMP-8 (also known as collagenase II, neutrophil collagenase, or EC 3.4.24.34), MMP-9 (also known as gelatinase B, 92kDa gelatinase, or EC 3.4.24.35), MMP-10 (also known as stromelysin 2 or EC 3.4.24.22), MMP-1 I (also known as stromelysin 3), MMP-12 (also known as metalloelastase, human macrophage elastase or HME), MMP- 13 (also known as collagenase 111), and MMP- 14 (also known as MT1-MMP or membrane MMP). *See, generally*, Woessner, J.F., "The Matrix Metalloprotease Family" in *Matrix Metalloproteinases*, pp.1-14 (Edited by Parks, W.C. & Mecham, R.P., Academic Press, San Diego, CA 1998).

[6] Excessive breakdown of connective tissue by MMPs is a feature of many pathological conditions. Inhibition of MMPs therefore provides a control mechanism for tissue decomposition to prevent and/or treat these pathological conditions. Such pathological conditions generally include, for example, tissue destruction, fibrotic diseases, pathological matrix weakening, defective injury repair, cardiovascular diseases, pulmonary diseases, kidney diseases, liver diseases, ophthalmologic diseases, and diseases of the central nervous system. Specific examples of such conditions include, for example, rheumatoid arthritis, osteoarthritis, septic arthritis, multiple sclerosis, a decubitis ulcer, corneal ulceration, epidermal ulceration, gastric ulceration, tumor metastasis, tumor invasion, tumor angiogenesis, periodontal disease, liver cirrhosis, fibrotic lung disease, emphysema, otosclerosis, atherosclerosis, proteinuria, coronary thrombosis, dilated cardiomyopathy, congestive heart failure, aortic aneurysm, epidermolysis bullosa, bone disease, Alzheimer's disease, defective injury repair *(e.g.,* weak repairs, adhesions such as post-surgical adhesions, and scarring), post-myocardial infarction, bone disease, and chronic obstructive pulmonary disease.

[7] Matrix metalloproteinases also are involved in the biosynthesis of tumor necrosis factors (TNFs). Tumor necrosis factors are implicated in many pathological conditions. TNF-α, for example, is a cytokine that is presently thought to be produced

initially as a 28 kD cell-associated molecule. It is released as an active, 17 kD form that can mediate a large number of deleterious effects *in vitro* and *in* vivo. TNF-α can cause and/or contribute to the effects of inflammation (*e.g.*, rheumatoid arthritis), autoimmune disease, graft rejection, multiple sclerosis, fibrotic diseases, cancer, infectious diseases (*e.g.*, malaria, mycobacterial infection, meningitis, etc.), fever, psoriasis, cardiovascular diseases (*e.g.*, post-ischemic reperfusion injury and congestive heart failure), pulmonary diseases, hemorrhage, coagulation, hyperoxic alveolar injury, radiation damage, and acute phase responses like those seen with infections and sepsis and during shock *(e.g.*, septic shock and hemodynamic shock). Chronic release of active TNF-α can cause cachexia and anorexia. TNF-α also can be lethal.

[8] Inhibiting TNF (and related compounds) production and action is an important clinical disease treatment. Matrix metalloproteinase inhibition is one mechanism that can be used. MMP *(e.g.*, collagenase, stromelysin, and gelatinase) inhibitors, for example, have been reported to inhibit TNF-α release. *See, e.g.*, Gearing et al. *Nature* 376, 555-557 (1994). *See also*, McGeehan et al. *See also*, *Nature* 376, 558-561 (1994). MMP inhibitors also have been reported to inhibit TNF-α convertase, a metalloproteinase involved in forming active TNF-α. *See, e.g.*, WIPO Int'l Pub. No. WO 94/24140. *See also*, WIPO Int'l Pub. No. WO 94/02466. *See also*, WIPO Int'l Pub. No. WO 97/20824.

[9] Matrix metalloproteinases also are involved in other biochemical processes in mammals. These include control of ovulation, post-partum uterine involution, possibly implantation, cleavage of APP (β-amyloid precursor protein) to the ainyloid plaque, and inactivation of (α_I-protease inhibitor (α_I -PI). Inhibiting MMPs therefore may be a mechanism that may be used to control of fertility. In addition, increasing and maintaining the levels of an endogenous or administered serine protease inhibitor *(e.g.*, α_I -PI) supports the treatment and prevention of pathological conditions such as emphysema, pulmonary diseases, inflammatory diseases, and diseases of aging *(e.g.*, loss of skin or organ stretch and resiliency).

[10] Numerous metalloproteinase inhibitors are known. *See, generally*, Brown, P.D., "Synthetic Inhibitors of Matrix Metalloproteinases," in *Matrix Metalloproteinases*,

pp. 243-61 (Edited by Parks, W.C. & Mecham, R.P., Academic Press, San Diego, CA 1998).

[11] Metalloproteinase inhibitors include, for example, natural biochemicals, such as tissue inhibitor of metalloproteinase (TIMP), α2-macroglobulin, and their analogs and derivatives. These are high-molecular-weight protein molecules that form inactive complexes with metalloproteinases.

[12] A number of smaller peptide-like compounds also have been reported to inhibit metalloproteinases. Mercaptoamide peptidyl derivatives, for example, have been reported to inhibit angiotensin converting enzyme (also known as ACE) *in vitro* and *in vivo*. ACE aids in the production of angiotensin II, a potent pressor substance in mammals. Inhibiting ACE leads to lowering of blood pressure.

[13] A wide variety of thiol compounds have been reported to inhibit MMPs. *See, e.g.*, W095/12389. *See also*, W096/11209. *See also*, U.S. Patent No. 4,595,700. *See also*, U.S. Patent No. 6.013,649.

[14] A wide variety of hydroxamate compounds also have been reported to inhibit MMPs. Such compounds reportedly include hydroxamates having a carbon backbone. *See, e.g.*, WIPO Int'l Pub. No. *WO* 95/29892. *See also*, WIPO Int'l Pub. No. WO 97/24117. *See also*, WIPO Int'l Pub. No. WO 97/49679. *See also*, European Patent No. EP 0 780 386. Such compounds also reportedly include hydroxamates having peptidyl backbones or peptidomimetic backbones. *See, e.g*, WIPO Int'l Pub. No. WO 90/05719. *See also*, WIPO Int'l Pub. No. WO 93/20047. *See also*, WIPO Int'l Pub. No. WO 95/09841. *See also*, WIPO Int'l Pub. No. WO 96/06074. *See also*, Schwartz et al., Progr. *Med. Chem.*, 29:271-334(1992). *See also*, Rasmussen et al., *PharmacoL Ther.*, 75(l): 69-75 (1997). *See also*, Denis et al., *Invest New Drugs*, 15(3): 175-185 (1997). Various piperazinylsulfonylmethyl hydroxamates and piperidinylsulfonylmethyl hydroxamates have additionally been reported to inhibit MMPs. *See*, WIPO Int'l Pub. No. WO 00/46221. And various aromatic sulfone hydroxamates have been reported to inhibit MMPs. *See*, WIPO Int'l Pub. No. WO 99/25687. *See also*, WIPO Int'l Pub. No. WO 00/50396. *See also*, WIPO Int'l Pub. No. WO 00/69821.

[15] It is often advantageous for an MMP inhibitor drug to target a certain MMP(s) over another MMP(s). For example, it is typically preferred to inhibit MMP-2,

MMP-3, MMP-9, and/or MMP-13 (particularly MMP-13) when treating and/or preventing cancer, inhibiting of metastasis, and inhibiting angiogenesis. It also is typically preferred to inhibit MMP-13 when preventing and/or treating osteoarthritis. *See, e.g.*, Mitchell et al., J *Clin. Invest.*, 97:761-768 (1996). *See also*, Reboul et al., *J Clin. Invest.*, 97:2011-2019 (1996). Normally, however, it is preferred to use a drug that has little or no inhibitory effect on MMP-1 and MMP-14. This preference stems from the fact that both MMP-1 and MMP-14 are involved in several homeostatic processes, and inhibition of MMP-1 and/or MMP-14 consequently tends to interfere with such processes.

[16] Many known MMP inhibitors exhibit the same or similar inhibitory effects against each of the MMPs. For example, batimastat (a peptidomimetic hydroxamate) has been reported to exhibit IC_{50} values of from about 1 to about 20 nM against each of MMP-1, MMP-2, MMP-3, MMP-7, and MMP-9. Marimastat (another peptidomimetic hydroxamate) has been reported to be another broad-spectrum MMP inhibitor with an enzyme inhibitory spectrum similar to batimastat, except that Marimastat reportedly exhibited an IC_{50} value against MMP-3 of 230 nM. *See* Rasmussen et al., *Pharmacol. Ther.*, 75(1): 69-75 (1997).

[17] Meta analysis of data from Phase I/II studies using Marimastat in patients with advanced, rapidly progressive, treatment-refractory solid tumor cancers (colorectal, pancreatic, ovarian, and prostate) indicated a dose-related reduction in the rise of cancer-specific antigens used as surrogate markers for biological activity. Although Marimastat exhibited some measure of efficacy via these markers, toxic side effects reportedly were observed. The most common drug-related toxicity of Marimastat in those clinical trials was musculoskeletal pain and stiffness, often commencing in the small joints in the hands, and then spreading to the arms and shoulder. A short dosing holiday of 1-3 weeks followed by dosage reduction reportedly permits treatment to continue. *See* Rasmussen et al., *Pharmacol. Ther.*, 75(l): 69-75 (1997). It is thought that the lack of specificity of inhibitory effect among the MMPs may be the cause of that effect.

[18] Another enzyme implicated in pathological conditions associated with excessive degradation of connective tissue is aggrecanase, particularly aggrecanase-1 (also known as ADAMTS-4). Specifically, articular cartilage contains large amounts of the proteoglycan aggrecan. Proteoglycan aggrecan provides mechanical properties that help articular cartilage in withstanding compressive deformation during joint articulation. The

loss of aggrecan fragments and their release into synovial fluid caused by proteolytic cleavages is a central pathophysiological event in osteoarthritis and rheumatoid arthritis. It has been reported that two major cleavage sites exist in the proteolytically sensitive interglobular domains at the N-terminal region of the aggrecan core protein. One of those sites has been reported to be cleaved by several matrix metalloproteases. The other site, however, has been reported to be cleaved by aggrecanase-1. Thus, inhibiting excessive aggrecanase activity provides an additional and/or alternative prevention or treatment method for inflammatory conditions. *See generally*, Tang, B. L., "ADAMTS: A Novel Family of Extracellular Matrix Proteases," *Int'l Journal of Biochemistry & Cell Biology*, 33, pp. 33-44 (2001). Such diseases reportedly include, for example, osteoarthritis, rheumatoid arthritis, joint injury, reactive arthritis, acute pyrophosphate arthritis, and psoriatic arthritis. *See, e.g.*, European Patent Application Publ. No. EP 1 081 137 A1.

[19] In addition to inflammatory conditions, there also is evidence that inhibiting aggrecanase may be used for preventing or treating cancer. For example, excessive levels of aggrecanase-1 reportedly have been observed with a ghoma cell line. It also has been postulated that the enzymatic nature of aggrecanase and its similarities with the MMPs would support tumor invasion, metastasis, and angiogenesis. *See* Tang, *Int'l Journal of Biochemistry & Cell Biology*, 33, pp. 33-44 (2001).

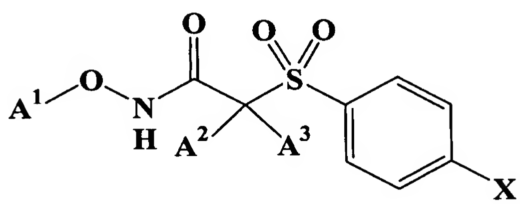
[20] Various hydroxamate compounds have been reported to inhibit aggrecanase-1. Such compounds include, for example, those described in European Patent Application Publ. No. EP 1 081 137 A1. Such compounds also include, for example, those described in WIPO PCT Int'l Publ. No. WO 00/09000. Such compounds further include, for example, those described in WIPO PCT Int'l Publ. No. WO 00/59874.

[21] In view of the importance of hydroxamate compounds in the prevention or treatment of several pathological conditions and the lack of enzyme specificity exhibited by two of the more potent MMP-inhibitor drugs that have been in clinical trials, there continues to be a need for hydroxamates having greater enzyme specificity (preferably toward MMP-2, MMP-9, MMP- 13, and/or aggrecanase (particularly toward MMP-13 in some instances, toward both MMP-2 and MMP-9 in other instances, and aggrecanase in yet other instances), while exhibiting little or no inhibition of MMP-1 and/or MMP-14. The following disclosure describes hydroxamate compounds that tend to exhibit such desirable activities.

SUMMARY OF THE INVENTION

[22] This invention is directed to hydroxamate compounds (and salts thereof) that inhibit pathological protease activity (particularly compounds that inhibit MMP-2, MMP-9, MMP- 13, and/or aggrecanase activity), while generally exhibiting relatively little or no inhibition against MMP-1 and MMP-14 activity. This invention also is directed to a method for inhibiting MMP activity and/or aggrecanase activity, particularly pathological MMP and/or aggrecanase activity. Such a method is particularly suitable to be used with mammals, such as humans, other primates (*e.g.*, monkeys, chimpanzees. etc.), companion animals (*e.g.*, dogs, cats, horses. etc.), farm animals (*e.g.*, goats, sheep, pigs, cattle, etc.), laboratory animals (*e.g.*, mice, rats, etc.), and wild and zoo animals (*e.g.*, wolves, bears, deer, etc.).

[23] Briefly, therefore, the invention is directed in part to a compound or salt thereof. The compound has a structure corresponding to Formula I:



I

Here:

A^1 is -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), or aminoalkyl(thiocarbonyl). Except where A^1 is -H, any member of this group optionally is substituted (*i.e.*, it may be either unsubstituted or substituted).

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members.

[24] In a preferred embodiment of the invention, X is -E^1-E^2-E^3-E^4-E^5. In this embodiment:

E^1 is -O-, -$S(O)_2$-, -S(O)-, -S-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-.

E^2 forms a link of at least 2 carbon atoms between E^1 and E^3. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^3 is -C(O)-, -O-(CO)-, -C(O)-O-, -C(NR^3)-, -N(R^4)-, -C(O)-N(R^4)-, -N(R^4)-C(O)-, -N(R^4)-C(O)-N(R^5)-, -S-, -S(O)-, -N(R^4)-$S(O)_2$-, -$S(O)_2$-N(R^4)-, -C(O)-N(R^4)-N(R^5)-C(O)-, -C(R^4)(R^6)-C(O)-, or -C(R^7)(R^8)-.

E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

E^5 is -H, -OH, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Except where E^5 is except -H or -OH, any member of this group optionally is substituted. E^5 is not -H when both E^3 is -C(R^7)(R^8)- and E^4 is a bond.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

R^3 is -H or -OH.

R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except for -H, any member of this group optionally is substituted. Neither R^4 nor R^5 forms a ring structure with E^2, E^4, or E^5.

R^6 is -CN or -OH.

R^7 is -H, halogen, -OH, alkyl, alkoxy, or alkoxyalkyl. The alkyl, alkoxy, and alkoxyalkyl optionally are substituted.

R^8 is -OH or alkoxy. The alkoxy optionally is substituted.

[25] In another preferred embodiment of the invention, X is -E^1-E^2-E^3-E^4-E^5. In this embodiment:

E^1 is -O-, -$S(O)_2$-, -S(O)-, -S-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-.

E^2 forms a link of at least 2 carbon atoms between E^1 and E3. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^3 is carbocyclyl or heterocyclyl. The carbocyclyl and heterocyclyl have 5 or 6 ring members and optionally are substituted.

E^4 is a bond, alkyl, alkenyl, -O-, or -N(R^3)-. The alkyl and alkenyl optionally are substituted.

E^5 is carbocyclyl or heterocyclyl. The carbocyclyl and heterocyclyl optionally are substituted.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

R^3 is -H or alkyl. The alkyl optionally is substituted.

[26] In another preferred embodiment of the invention, X is -E^1-E^2-C(E^6)=C(E^7)-E^3-E^4-E^5. In this embodiment:

E^1 is -O-, -S(O)$_2$-, -S(O)-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-.

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^4 is a bond or alkyl. The alkyl optionally is substituted.

E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

E^6 is -H, halogen, or alkyl. The alkyl optionally is substituted.

E^7 is -H, alkyl, alkenyl, alkynyl, -S(O)$_2$-R^3, -NO_2, -C(O)-N(R^3)(R^4), -(C)(OR^3), carbocyclyl, carbocyclylalkyl, alkoxycarbocyclyl, -CN, -C=N-OH, or -C=NH. The alkyl, alkenyl, alkynyl, carbocyclyl, carbocycylalkyl, and alkoxycarbocyclyl optionally are substituted.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^4, E^5, E^6, or E^7.

R^3 and R^4 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl. Except where the member is -H, any member of this group optionally is substituted.

[27] In another preferred embodiment of the invention, X is $-E^1-E^2-E^3-E^4-E^5$. In this embodiment:

E^1 is -O-, $-S(O)_2-$, -S(O)-, $-N(R^3)-$, $-C(O)-N(R^3)-$, $-N(R^3)-C(O)-$, or $-C(R^1)(R^2)-$.

E^2 is a bond, alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Except where the member is a bond, any member of such group optionally is substituted.

E^3 is carbonylpyrrollidinyl. The carbonylpyrrollidinyl optionally is substituted.

E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally and substituted.

E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

[28] In another preferred embodiment of the invention, X is $-E^1-E^2-E^5$. In this embodiment:

E^1 is -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, alkyl, and haloalkyl.

E^5 is alkyl, alkenyl, alkynyl, cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, or cyclohexadienyl. The cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, and cyclohexadienyl optionally are substituted. The alkyl, alkenyl, and alkynyl (a) contain at least 4 carbon atoms, and (b)

optionally are substituted with one or more substituents selected from the group consisting of -OH, -NO_2, -CN, and halogen.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^5.

[29] In another preferred embodiment of the invention, X is -E^1-E^2-E^3-E^4-E^5. In this embodiment:

E^1 is -O-, -$S(O)_2$-, -S(O)-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-.

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^3 is carbonylpiperidinyl. The carbonylpiperidinyl optionally is substituted.

E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

[30] In another preferred embodiment of the invention, X is -E^1-E^2-E^5. In this embodiment:

E^1 is -O-, -$S(O)_2$-, -S(O)-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-.

E^2 forms a link of at least 3 carbon atoms between E^1 and E^5. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^5 is optionally-substituted heterocyclyl, optionally-substituted fused-ring carbocyclyl, or substituted single-ring carbocyclyl.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^5.

[31] In another preferred embodiment of the invention, X is $-E^1-E^2-E^5$. In this embodiment:

E^1 is -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

E^2 forms a link of at least 4 carbon atoms between E^1 and E^5. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^5 is -OH or optionally-substituted carbocyclyl.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^5.

[32] In another preferred embodiment of the invention, X is $-E^1-E^2-O-E^4-E^5$. In this embodiment:

E^1 is $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^4, or E^5.

[33] In another preferred embodiment of the invention, X is $-O-E^2-O-E^5$. In this embodiment:

E^2 comprises at least 3 carbon atoms. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^5 is -H, alkyl, alkenyl, alkynyl, alkoxyalkyl, carbocyclyl, carbocyclylalkoxyalkyl, heterocyclyl, heterocyclylalkyl, or heterocyclylalkoxyalkyl. The alkyl, alkenyl, alkynyl, and alkoxyalkyl optionally are substituted with one or more substituents independently selected from the

group consisting of halogen, -OH, $-NO_2$, and -CN. the carbocyclyl, carbocyclylalkoxyalkyl, heterocyclyl, heterocyclylalkyl, and heterocyclylalkoxyalkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, halogen-substituted alkoxyalkyl, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl.

R^1 and R^2 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H., any member of this group optionally is substituted with one or more halogen.

R^3 is -H, alkyl, $-O-R^4$, $-N(R^4)(R^5)$, carbocyclylalkyl, or heterocyclylalkyl. The alkyl, carbocyclylalkyl, and heterocyclylalkyl optionally are substituted with one or more halogen.

R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

[34] In another preferred embodiment of the invention, X is $-O-E^2-O-E^4-E^5$. In this embodiment:

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted. An atom in E^2 optionally is bound to an atom in E^5 to form a ring.

E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

E^5 is:

an optionally-substituted radical selected from the group consisting of alkenyl, alkynyl, alkoxy, alkoxyalkyl, fused-ring carbocyclyl, and heterocyclyl;

single-ring carbocyclyl substituted with one or more substituents independently selected from the group consisting of -OH, $-NO_2$, -CN, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$,

carbocyclyl, halocarbocyclyl, carbocyclylalkyl, halogen-substituted carbocyclylalkyl, heterocyclyl, haloheterocyclyl, heterocyclylalkyl, and halogen-substituted heterocyclylalkyl; or

single-ring carbocyclyl having multiple substitutions.

R^1 and R^2 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

R^3 is -H, alkyl, -O-R^4, -N(R^4)(R^5), carbocyclylalkyl, or heterocyclylalkyl. The alkyl, carbocyclylalkyl, and heterocyclylalkyl optionally are substituted with one or more halogen.

R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

[35] In another preferred embodiment of the invention, X is -E^1-E^2-S(O)$_2$-E^4-E^5. In this embodiment:

E^1 is -S(O)$_2$-, -S(O)-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-.

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^4, or E^5.

[36] In another preferred embodiment of the invention, X is -O-E^2-S(O)$_2$-E^4-E^5. In this embodiment:

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^4 is alkyl or alkenyl. The alkyl and alkenyl optionally are substituted.

E^5 is -H, alkyl, alkenyl, alkynyl, alkoxy, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[37] In another preferred embodiment of the invention, X is -O-E^2-$S(O)_2$-E^5. In this embodiment:

E^2 comprises less than 5 carbon atoms. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

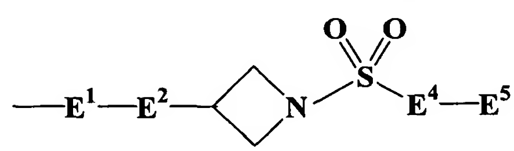
E^5 is alkyl, alkenyl, alkynyl, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[38] In another preferred embodiment of the invention, X is -O-E^2-$S(O)_2$-E^5. In this embodiment:

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^5 is alkyl, alkenyl, alkynyl, alkoxyalkyl, saturated carbocyclyl, partially saturated carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[39] In another preferred embodiment of the invention, X is:



In this embodiment:

E^1 -$S(O)_2$-, -S(O)-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-.

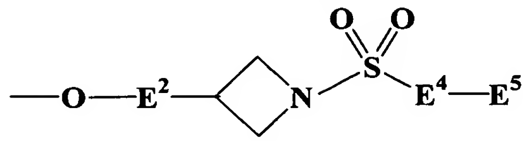
E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^4 is a bond, alkyl, or alkenyl, The alkyl and alkenyl optionally are substituted.

E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^4, or E^5.

[40] In another preferred embodiment of the invention, X is:



In this embodiment:

E^2 is a bond, alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

E^5 is substituted carbocyclyl or optionally-substituted heterocyclyl. The carbocyclyl is substituted with:

two or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, halogen-substituted alkoxyalkyl, -N(R^3)(R^4), -C(O)(R^5), -S-R^3, -S(O)$_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl; or

a substituent selected from the group consisting of halogen, -OH, -NO_2, -CN, -C(O)-O-R^3, -S-R^3, -S(O)$_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl.

The heterocyclyl, on the other hand, optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, halogen-substituted alkoxyalkyl, -N(R^3)(R^4), -C(O)(R^5), -S-R^3, -S(O)$_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl.

R^3 and R^4 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

R^5 is -H, alkyl, -O-R^6, -N(R^6)(R^7), carbocyclylalkyl, or heterocyclylalkyl. The alkyl, carbocyclylalkyl, and heterocyclylalkyl optionally are substituted with one or more halogen.

R^6 and R^7 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

[41] In another preferred embodiment of the invention, X is -E^1-E^2-E^5. In this embodiment:

E^1 is -O-, -S(O)$_2$-, -S(O)-, -S-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-.

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of such group optionally is substituted.

E^5 is substituted heterocyclyl.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted.

Neither R^1 nor R^2 forms a ring structure with E^5.

[42] In another preferred embodiment of the invention, X is -E^1-E^2-E^5. In this embodiment:

E^1 is -O-, -S(O)$_2$-, -S(O)-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-.

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of such group optionally is substituted. In addition, E^2 comprises at least two carbon atoms.

E^5 is optionally-substituted heterocyclyl.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substitute.

Neither R^1 nor R^2 forms a ring structure with E^5.

[43] In another preferred embodiment of the invention, X is -E^1-E^2-E^3-E^4-E^5. In this embodiment:

E^1 is -O-, -S(O)$_2$-, -S(O)-, -S-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-.

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of such group optionally is substituted.

E^3 is -C(O)-, -O-(CO)-, -C(O)-O-, -C(NR^3)-, -N(R^4)-, -N(R^4)-C(NR^3)-, -C(NR^3)-N(R^4)-, -C(O)-N(R^4)-, -N(R^4)-C(O)-, -N(R^4)-C(O)-N(R^5)-, -S-, -S(O)-, -N(R^4)-S(O)$_2$-, -S(O)$_2$-N(R^4)-, -C(O)-N(R^4)-N(R^5)-C(O)-, -C(R^4)(R^6)-C(O)-, or -C(R^7)(R^8)-.

E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

E^5 is carbocyclyl or heterocyclyl. The carbocyclyl and heterocyclyl are:

substituted with a substituent selected from the group consisting of optionally-substituted carbocyclyl, optionally-substituted carbocyclylalkyl, optionally-substituted heterocyclyl, and optionally-substituted heterocyclylalkyl; and

optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO$_2$, -CN, alkyl, alkoxy, alkoxyalkyl, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, carbocyclyl, carbocyclylalkyl, haloalkyl, haloalkoxy, halogen-substituted alkoxyalkyl, halocarbocyclyl, halogen-substituted carbocyclylalkyl, hydroxycarbocyclyl, and heteroaryl.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl, wherein the alkyl optionally is substituted.

R^3 is -H or -OH.

R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl, wherein any member (except -H) of such group optionally is substituted.

R^6 is -CN or -OH.

R^7 is -H, halogen, -OH, alkyl, alkoxy, or alkoxyalkyl. The alkyl, alkoxy, and alkoxyalkyl optionally are substituted.

R^8 is -OH or alkoxy. The alkoxy optionally is substituted.

R^{11} and R^{12} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and

heterocyclyl-C_1-C_8-alkyl. Any member (except -H) of such group optionally is substituted with one or more halogen.

R^{13} is -H, C_1-C_8-alkyl, -O-R^{14}, -N(R^{14})(R^{15}), carbocyclyl-C_1-C_8-alkyl, heterocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, or halogen-substituted heterocyclyl-C_1-C_8-alkyl.

R^{14} and R^{15} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Any member (except -H) of such group optionally is substituted with one or more halogen.

Neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

Neither R^4 nor R^5 forms a ring structure with E^2, E^4, or E^5.

[44] This invention also is directed, in part, to a method for preventing or treating a condition associated with pathological matrix metalloprotease activity in a mammal having the condition or predisposed to having the condition. The method comprises administering an above-described compound or a pharmaceutically acceptable salt thereof to the mammal in an amount that is therapeutically-effective to prevent or treat the condition.

[45] This invention also is directed, in part, to a method for preventing or treating a pathological condition in a mammal having the condition or predisposed to having the condition. The method comprises administering an above-described compound or a pharmaceutically acceptable salt thereof to the mammal in an amount that is therapeutically-effective to prevent or treat the condition. In this embodiment, the pathological condition comprises tissue destruction, a fibrotic disease, pathological matrix weakening, defective injury repair, a cardiovascular disease, a pulmonary disease, a kidney disease, a liver disease, an ophthalmologic disease, and a central nervous system disease.

[46] This invention also is directed, in part, to a method for preventing or treating a pathological condition in a mammal having the condition or predisposed to having the condition. The method comprises administering an above-described compound or a pharmaceutically acceptable salt thereof to the mammal in an amount that is therapeutically-effective to prevent or treat the condition. In this embodiment, the pathological condition comprises osteoarthritis, rheumatoid arthritis, septic arthritis, tumor

invasion, tumor metastasis, tumor angiogenesis, a decubitis ulcer, a gastric ulcer, a corneal ulcer, periodontal disease, liver cirrhosis, fibrotic lung disease, otosclerosis, atherosclerosis, multiple sclerosis, dilated cardiomyopathy, epidermal ulceration, epidermolysis bullosa, aortic aneurysm, defective injury repair, an adhesion, scarring, congestive heart failure, post myocardial infarction, coronary thrombosis, emphysema, proteinuria, Alzheimer's disease, bone disease, and chronic obstructive pulmonary disease.

[47] This invention also is directed, in part, to a method for preventing or treating a condition associated with pathological TNF-α convertase activity in a mammal having the condition or predisposed to having the condition. The method comprises administering an above-described compound or a pharmaceutically acceptable salt thereof to the mammal in an amount that is therapeutically-effective to prevent or treat the condition.

[48] This invention also is directed, in part, to a method for preventing or treating a condition associated with pathological aggrecanase activity in a mammal having the condition or predisposed to having the condition. The method comprises administering an above-described compound or a pharmaceutically acceptable salt thereof to the mammal in an amount that is therapeutically-effective to prevent or treat the condition.

[49] This invention also is directed, in part, to pharmaceutical compositions comprising a therapeutically-effective amount of an above-described compound or a pharmaceutically-acceptable salt thereof.

[50] This invention also is directed, in part, to a use of an above-described compound or a pharmaceutically acceptable salt thereof to prepare a medicament for treating a condition associated with pathological matrix metalloprotease activity.

[51] This invention also is directed, in part, to a use of an above-described compound or a pharmaceutically acceptable salt thereof to prepare a medicament for treating a condition associated with pathological TNF-α convertase activity.

[52] This invention also is directed, in part, to a use of an above-described compound or a pharmaceutically acceptable salt thereof to prepare a medicament for treating a condition associated with pathological aggrecanase activity.

[53] Further benefits of Applicants' invention will be apparent to one skilled in the art from reading this patent.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

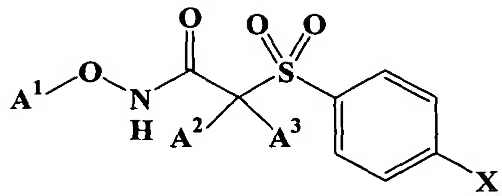
[54] This detailed description of preferred embodiments is intended only to acquaint others skilled in the art with Applicants' invention, its principles, and its practical application so that others skilled in the art may adapt and apply the invention in its numerous forms, as they may be best suited to the requirements of a particular use. This detailed description and its specific examples, while indicating preferred embodiments of this invention, are intended for purposes of illustration only. This invention, therefore, is not limited to the preferred embodiments described in this patent, and may be variously modified.

A. Compounds of This Invention

[55] In accordance with this invention, it has been found that certain aromatic sulfone hydroxamates tend to be effective for inhibiting MMPs, particularly those associated with excessive (or otherwise pathological) breakdown of connective tissue. Specifically, Applicants have found that these hydroxamates tend to be effective for inhibiting proteases (particularly MMP-2, MMP-9, MMP- 13, other MMP's associated with pathological conditions, and/or aggrecanase) that are often particularly destructive to tissue if present or generated in abnormally excessive quantities or concentrations. Moreover, Applicants have discovered that these hydroxamates tend to be selective toward inhibiting pathological protease activity, while avoiding excessive inhibition of other proteases (particularly MMP-1 and/or MMP-14) that are typically essential to normal bodily function *(e.g.,* tissue turnover and repair).

A-1. Preferred Compound Structures

[56] As noted above, the compound of this invention generally has a structure corresponding to Formula I:



I.

[57] A^1 is -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), or aminoalkyl(thiocarbonyl). Except where the member is -H, any member of this group optionally is substituted.

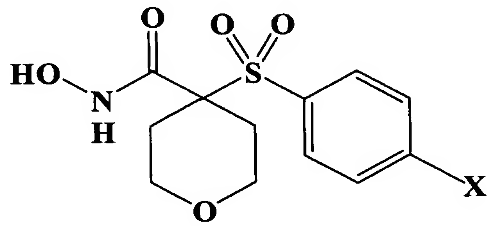
[58] In some preferred embodiments, A^1 is -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^A)(R^B)$-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), or $N(R^A)(R^B)$-C_1-C_8-alkyl(thiocarbonyl). R^A and R^B are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl.

[59] In generally more preferred embodiments, A^1 is -H.

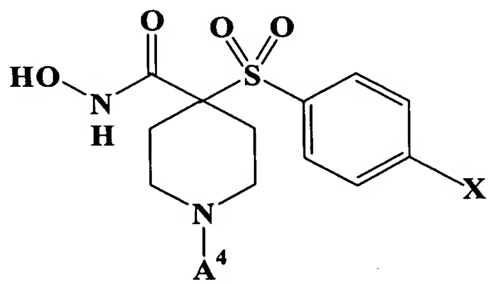
[60] A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members (*i.e.*, from 5 to 8 atoms are bound together to form the ring (or rings) of the heterocyclyl).

[61] In some preferred embodiments, A^2 and A^3, together with the carbon atom to which they both are attached, form an optionally-substituted heterocyclyl containing either 5 or 6 ring members.

[62] In some preferred embodiments, the compound corresponds in structure to one of the following formulas:



I-A



I-B

[63] A^4 is -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsulfoxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocyclylthioalkyl, carbocyclylsulfoxidoalkyl, carbocyclylsulfonylalkyl, carbocyclylthioalkenyl, carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocyclylthioalkyl, heterocyclylsulfoxidoalkyl, heterocyclylsulfonylalkyl, heterocyclylthioalkenyl, heterocyclylsulfoxidoalkenyl, heterocyclylsulfonylalkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclylalkylcarbonyl, heterocyclylcarbonylalkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl , aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, or aminoalkylsulfonyl. Except where the member is -H, any member of this group optionally is substituted.

[64] In some preferred embodiments, A^4 is -H, C_1-C_8-alkyl, C_1-C_8-alkylcarbonyl, C_1-C_8-alkylcarbonyl-C_1-C_8-alkyl, C_1-C_8-alkylcarbonyl-C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkoxycarbonyl-C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl-C_1-C_8-alkylcarbonyl, C_1-C_8-alkylsulfonyl, C_1-C_8-alkyliminocarbonyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, C_1-C_8-alkylthio-C_1-C_8-alkyl, C_1-C_8-alkylthio-C_2-C_8-alkenyl, C_1-C_8-alkylsulfoxido-C_1-C_8-alkyl, C_1-C_8-alkylsulfoxido-C_2-C_8-alkenyl, C_1-C_8-alkylsulfonyl-C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl-C_2-C_8-alkenyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocyclylthio-C_1-C_8-alkyl, carbocyclylthio-C_2-C_8-alkenyl, carbocyclylsulfoxido-C_1-C_8-alkyl, carbocyclylsulfoxido-C_2-C_8-alkenyl, carbocyclylsulfonyl-C_1-C_8-alkyl, carbocyclylsulfonyl-C_2-C_8-alkenyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, heterocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, heterocyclylcarbonyl, heterocyclylthio-C_1-C_8-alkyl, heterocyclylsulfoxido-C_1-C_8-alkyl, heterocyclylsulfonyl-C_1-C_8-alkyl, heterocyclylthio-C_2-C_8-alkenyl, heterocyclylsulfoxido-C_2-C_8-alkenyl, heterocyclylsulfonyl-C_2-C_8-alkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl-C_1-C_8-alkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonyl-C_1-C_8-alkyl, $N(R^C)(R^D)$-C_1-C_8-alkylcarbonyl, $N(R^C)(R^D)$-carbonyl , $N(R^C)(R^D)$-carbonyl-C_1-C_8-alkylcarbonyl, $N(R^C)(R^D)$-sulfonyl, $N(R^C)(R^D)$-sulfonyl-C_1-C_8-alkyl, $N(R^C)(R^D)$-C_1-C_8-alkyl, $N(R^C)(R^D)$-carbonyl-C_1-C_8-alkyl, or $N(R^C)(R^D)$-C_1-C_8-alkylsulfonyl. Any substitutable member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -CN, -C(O)-OH, -SH, $-SO_3H$, and NO_2.

[65] R^C and R^D are independently selected from the group consisting of -H, -OH, C_1-C_8-alkyl, C_1-C_8-alkyl-carbonyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkyl-thio-C_1-C_8-alkyl, C_1-C_8-alkyl-sulfoxido-C_1-C_8-alkyl, C_1-C_8-alkyl-sulfonyl-C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclylthio-C_1-C_8-alkyl,

carbocyclylsulfoxido-C_1-C_8-alkyl, carbocyclylsulfonyl-C_1-C_8-alkyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, heterocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, heterocyclylcarbonyl, heterocyclylthio-C_1-C_8-alkyl, heterocyclylsulfoxido-C_1-C_8-alkyl, heterocyclylsulfonyl-C_1-C_8-alkyl, aminocarbonyl-C_1-C_8-alkyl, C_1-C_8-alkyloxycarbonylamino-C_1-C_8-alkyl, and amino-C_1-C_8-alkyl. Except where the member is -H or OH, any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -CN, -C(O)-OH, -SH, $-SO_3H$, and NO_2. The nitrogen of the amino-C_1-C_8-alkyl optionally is substituted with 1 or 2 substituents independently selected from the group consisting of C_1-C_8-alkyl, C_1-C_8-alkylcarbonyl, carbocyclyl, and carbocyclyl-C_1-C_8-alkyl. No greater than one of R^C or R^D is -OH.

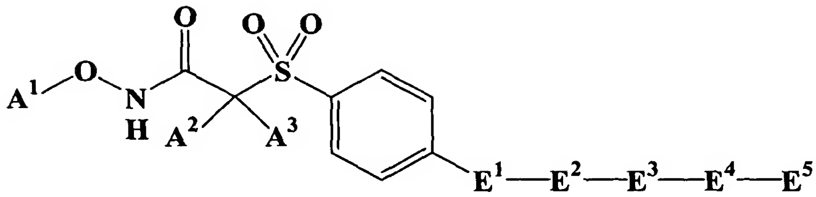
[66] In some preferred embodiments, A^4 is -H, C_1-C_6-alkyl (often preferably C_1-C_4-alkyl, and more preferably ethyl), C_1-C_6-alkoxy-C_1-C_6-alkyl (often preferably C_1-C_2-alkoxy-C_1-C_3-alkyl, and more preferably methoxyethyl), carbocyclyl (often preferably C_3-C_6-cycloalkyl or phenyl, and more preferably cyclopropyl), carbocyclyl-C_1-C_6-alkyl (often preferably C_3-C_6-cycloalkyl-C_1-C_3-alkyl or phenyl-C_1-C_3-alkyl, and more preferably cyclopropylmethyl or benzyl), C_1-C_6-alkylsulfonyl (often preferably C_1-C_2-alkylsulfonyl, and more preferably methylsulfonyl), C_3-C_6-alkenyl (often preferably C_3-C_4-alkenyl, and more preferably C_3-alkenyl), C_3-C_6-alkynyl (often preferably C_3-C_4-alkynyl, and more preferably C_3-alkynyl). Except where the member is -H, any member of these groups optionally is substituted with halogen, but more typically is preferably not substituted with halogen.

[67] In some preferred embodiments, A^4 is -H, ethyl, methoxyethyl, cyclopropyl, cyclopropylmethyl, or benzyl.

[68] X may be selected from a wide range of substituents. The following discussion describes several specific preferred embodiments encompassing the substituents that Applicants have found to be generally preferred.

Preferred Embodiment No. 1

[69] In some embodiments of this invention, the compound has a structure corresponding to Formula II:



II.

[70] A^1, A^2, and A^3 are as defined above for Formula I.

[71] E^1 is -O-, -S(O)$_2$-, -S(O)-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-. E^1 alternatively may be -S-.

[72] E^2 forms a link of at least 2 carbon atoms between E^1 and E^3. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[73] In some preferred embodiments, E^2 is C_2-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[74] In some preferred embodiments, E^2 is C_2-C_6-alkyl optionally substituted with one or more halogen.

[75] In some preferred embodiments, E^2 is C_2-C_6-alkyl.

[76] In some preferred embodiments, E^2 is C_2-C_6-alkyl.

[77] E^3 is -C(O)-, -O-(CO)-, -C(O)-O-, -C(NR^3)-, -N(R^4)-, -C(O)-N(R^4)-, -N(R^4)-C(O)-, -N(R^4)-C(O)-N(R^5)-, -S-, -S(O)-, -N(R^4)-S(O)$_2$-, -S(O)$_2$-N(R^4)-, -C(O)-N(R^4)-N(R^5)-C(O)-, -C(R^4)(R^6)-C(O)-, or -C(R^7)(R^8)-.

[78] E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

[79] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, or C_2-C_{20}-alkenyl. The C_1-C_{20}-alkyl andC_2-C_{20}-alkenyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen and carbocyclyl. This carbocyclyl, in turn, optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO$_2$, -CN, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl,

carbocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl.

[80] In some preferred embodiments, E^4 a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl. The C_1-C_3-alkyl, and C_2-C_3-alkenyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen and carbocyclyl. This carbocyclyl, in turn, optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[81] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl.

[82] E^5 is -H, -OH, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Except where E^5 is -H or -OH, any member of this group optionally is substituted. E^5 is not -H when both E^3 is -C(R^7)(R^8)- and E^4 is a bond.

[83] In some preferred embodiments, E^5 is -H, -OH, C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl. The carbocyclyl and heterocyclyl also optionally are substituted with one or more substituents independently selected from the group consisting of C_1-C_8-alkylcarbocyclyl, halogen-substituted C_1-C_8-alkylcarbocyclyl, hydroxycarbocyclyl, and heterocyclyl.

[84] In some preferred embodiments, E^5 is -H, -OH, C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halocarbocyclyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, C_1-C_6-alkylcarbocyclyl, halogen-substituted C_1-C_6-alkylcarbocyclyl, hydroxycarbocyclyl, and heteroaryl.

[85] In some preferred embodiments, E^5 is furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thiophenyl, dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxatriazolyl, dioxazolyl, oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl, dihydropyranyl, pyridinyl, piperidinyl, diazinyl, piperazinyl, triazinyl, oxazinyl, isoxazinyl, oxathiazinyl, oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl, diazepinyl, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinolinyl, carbazolyl, xanthenyl, or acridinyl. Such substituent optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted

C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, and halogen-substituted aryl-C_1-C_6-alkyl. Any member of such group also optionally is substituted with one or more substituent independent selected from the group consisting of C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

[86] In some preferred embodiments, E^5 is indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinolinyl, or pyridofuranyl. Such substituent optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl. Such substituent also optionally is substituted with one or more substituents independently selected from the group consisting of C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

[87] In some preferred embodiments, E^5 is benzazinyl, benzofuranyl, or tetrahydroisoquinolinyl. Such substituent optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, and halogen-substituted aryl-C_1-C_6-alkyl. Such substituent also optionally is substituted with one or more substituents independently selected from the group consisting of C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

[88] In some preferred embodiments, E^5 is indolyl, benzoxazolyl, benzothienyl, benzothiazolyl, or pyridofuranyl. Such substituent any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy,

C_1-C_6-alkoxy-C_1-C_6-alkyl, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, and halogen-substituted aryl-C_1-C_6-alkyl. Such substituent also optionally is substituted with one or more substituents independently selected from the group consisting of C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

[89] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

[90] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl.

[91] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[92] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, and C_1-C_6-alkyl.

[93] R^3 is -H or -OH.

[94] R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except for -H, any member of this group optionally is substituted. Neither R^4 nor R^5 forms a ring structure with E^2, E^4, or E^5.

[95] In some preferred embodiments, R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[96] In some preferred embodiments, R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[97] R^6 is -CN or -OH.

[98] R^7 is -H, halogen, -OH, alkyl, alkoxy, or alkoxyalkyl. The alkyl, alkoxy, and alkoxyalkyl optionally are substituted.

[99] In some preferred embodiments, R^7 is -H, halogen, -OH, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, or halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl.

[100] In some preferred embodiments, R^7 is -H, halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, or halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl.

[101] In some preferred embodiments, R^7 is -H, halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, or C_1-C_6-alkoxy-C_1-C_6-alkyl.

[102] R^8 is -OH or alkoxy. The alkoxy optionally is substituted.

[103] In some preferred embodiments, R^8 is -OH, C_1-C_8-alkoxy, or halo-C_1-C_8-alkoxy.

[104] In some preferred embodiments, R^8 is -OH, C_1-C_6-alkoxy, or halo-C_1-C_6-alkoxy.

[105] In some preferred embodiments, R^8 is -OH or C_1-C_6-alkoxy.

[106] R^{11} and R^{12} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[107] In some preferred embodiments, R^{11} and R^{12} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[108] R^{13} is -H, C_1-C_8-alkyl, -O-R^{14}, -N(R^{14})(R^{15}), carbocyclyl-C_1-C_8-alkyl, heterocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, or halogen-substituted heterocyclyl-C_1-C_8-alkyl.

[109] In some preferred embodiments, R^{13} is -H, C_1-C_6-alkyl, -O-R^{14}, -N(R^{14})(R^{15}), carbocyclyl-C_1-C_6-alkyl, heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl,

halogen-substituted carbocyclyl-C_1-C_6-alkyl, or halogen-substituted heterocyclyl-C_1-C_6-alkyl.

[110] In some preferred embodiments, R^{13} is -H, C_1-C_6-alkyl, -O-R^{14}, -N(R^{14})(R^{15}), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl.

[111] R^{14} and R^{15} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but typically is preferably not substituted with halogen.

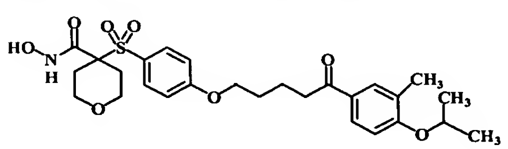
[112] In some preferred embodiments, R^{14} and R^{15} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but typically is preferably not substituted with halogen.

Preferred Embodiment No. 1-a: E^3 is -C(O)-

[113] In some embodiments, E^3 is -C(O)-.

[114] In some such embodiments, E^5 is optionally-substituted carbocyclyl, and often preferably optionally-substituted cycloalkyl or optionally-substituted aryl.

[115] In some preferred embodiments, for example, E^5 is optionally-substituted phenyl. Such compounds include, for example:



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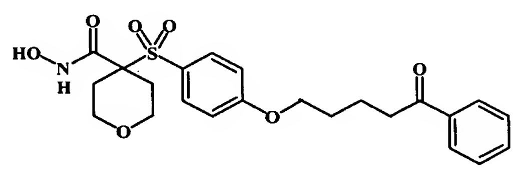

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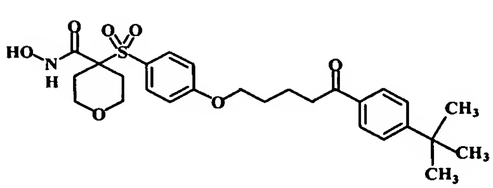

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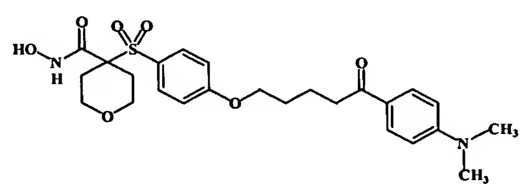

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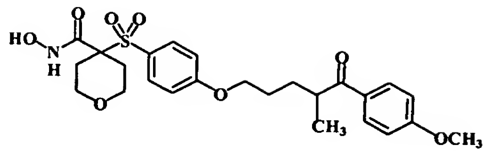

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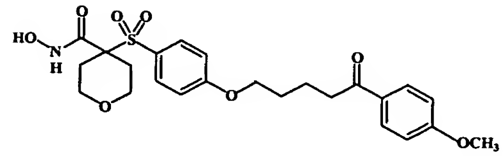

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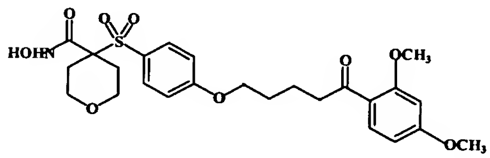

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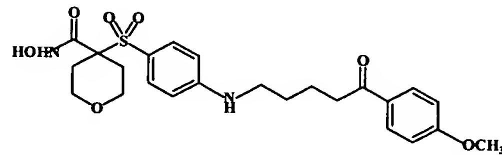

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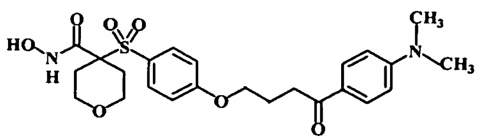

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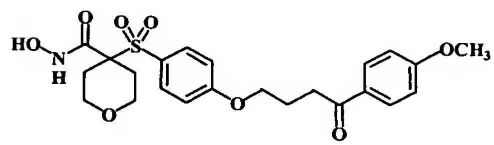
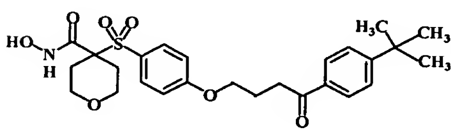
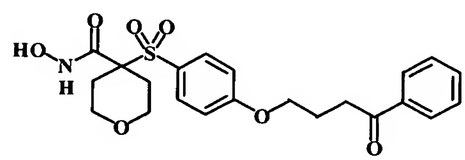


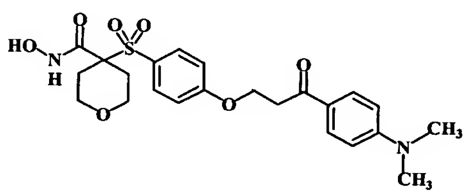
IIA-10



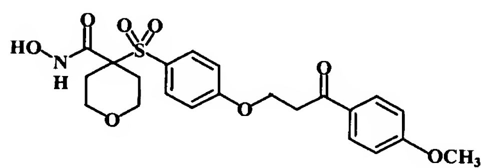
IIA-11



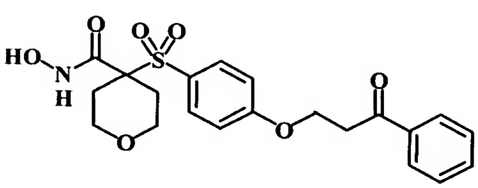
IIA-12



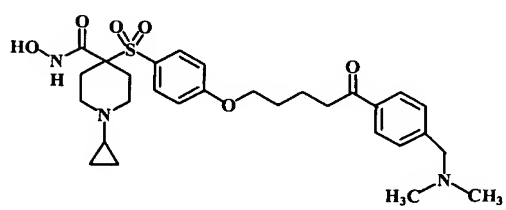
IIA-13



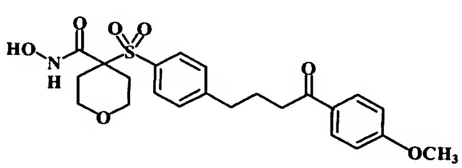
IIA-14



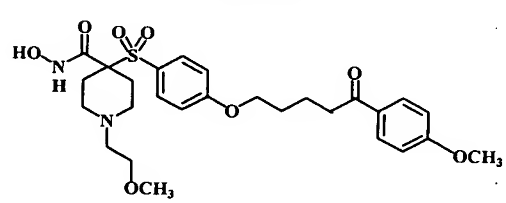
IIA-15



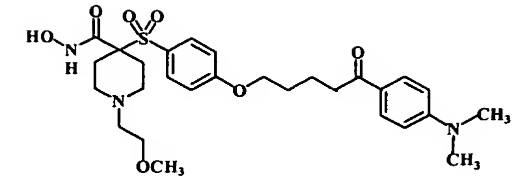
IIA-16



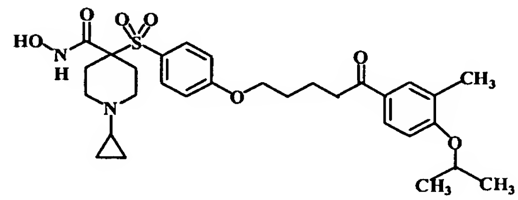
IIA-17



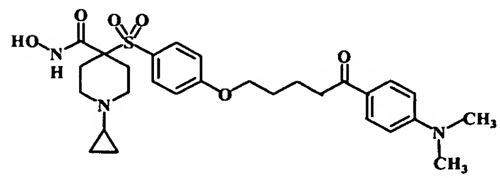
IIA-18



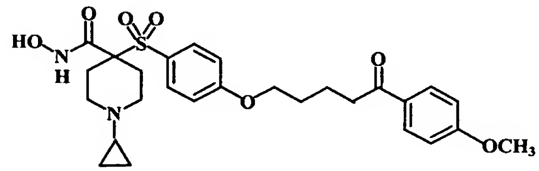
IIA-19



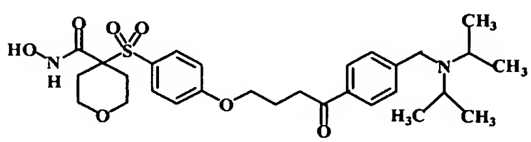
IIA-20



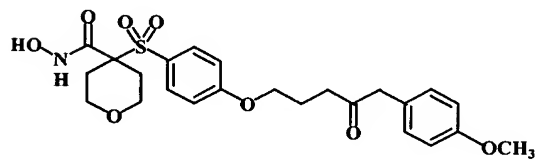
IIA-21



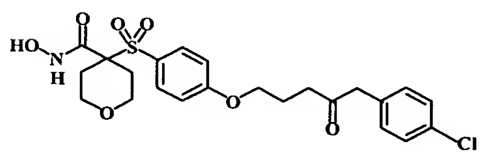
IIA-22



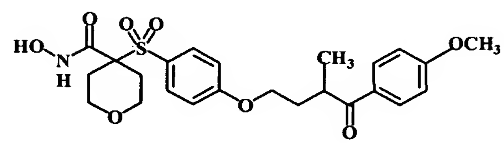
IIA-23



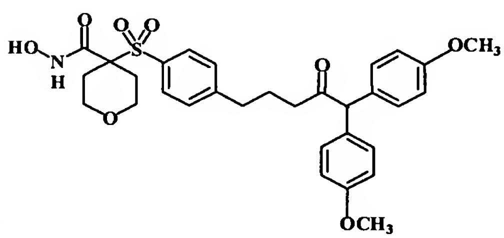
IIA-24



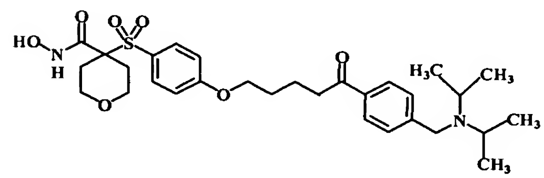
IIA-25



IIA-26



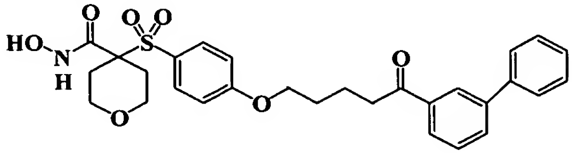
IIA-27



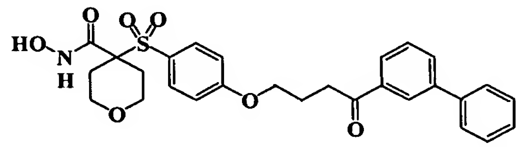
IIA-28

Such compounds also include compounds wherein E^5 is phenyl substituted with one or more substituents independently selected from the group consisting of aryl, haloaryl, aryl-C_1-C_6-alkyl, and halogen-substituted aryl-C_1-C_6-alkyl. Here, the phenyl also optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl,

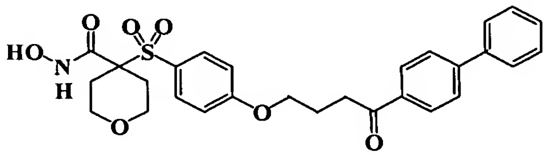
halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl. Such compounds include, for example:



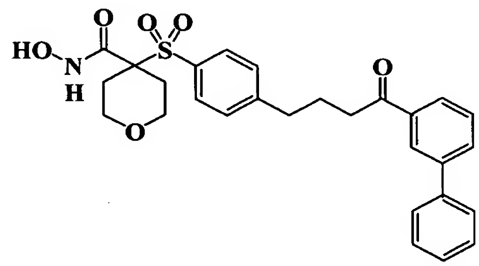
IIA-29



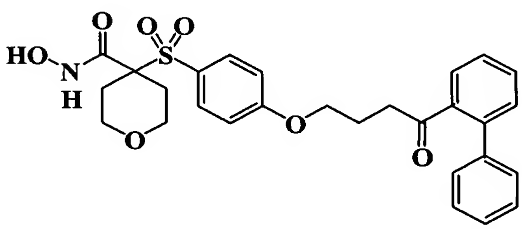
IIA-30



IIA-31

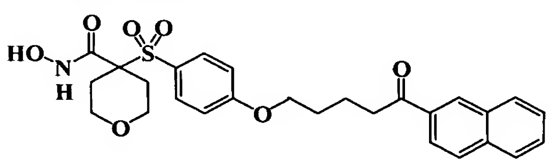


IIA-32

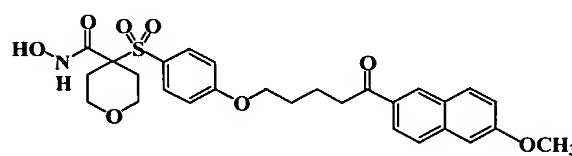


IIA-33

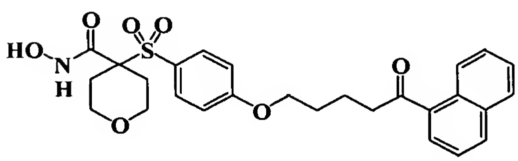
[116] In other preferred embodiments, E^5 is optionally-substituted naphthalenyl. Such compounds include, for example:



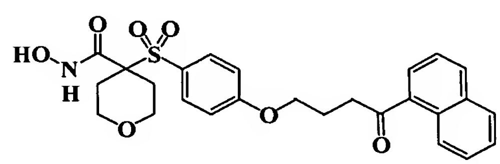
IIA-34



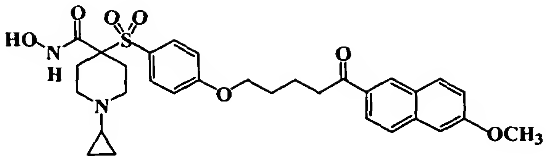
IIA-35



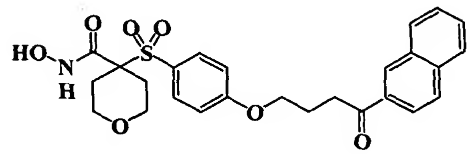
IIA-36



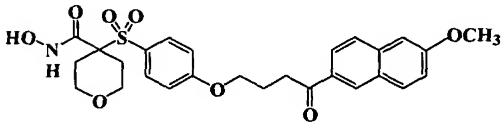
IIA-37



IIA-38

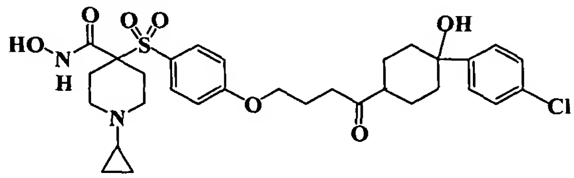


IIA-39



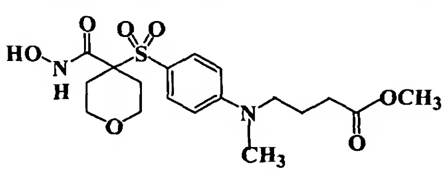
IIA-40

[117] In yet other preferred embodiments, E^5 is optionally-substituted C_5-C_6-cycloalkyl. Such compounds include, for example:

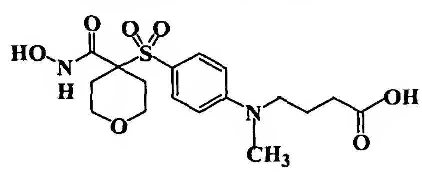


IIA-41.

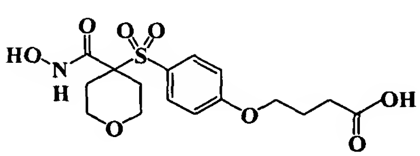
[118] In some preferred embodiments, E^5 is -H, -OH, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, or C_1-C_6-alkoxy-C_1-C_6-alkyl. The C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. Such compounds include, for example:



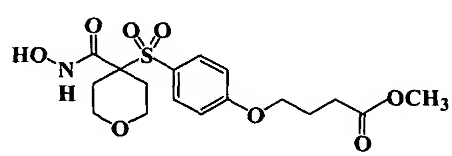
IIA-42



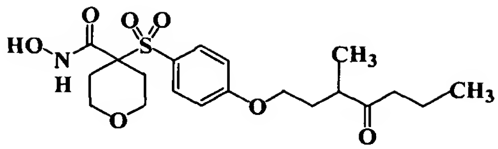
IIA-43



IIA-44

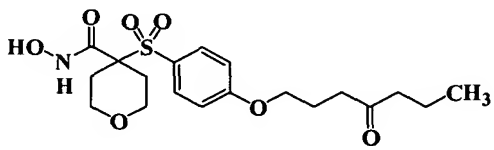


IIA-45

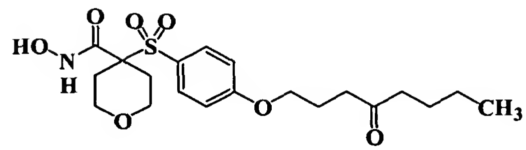


IIA-46

Other such compounds include, for example:

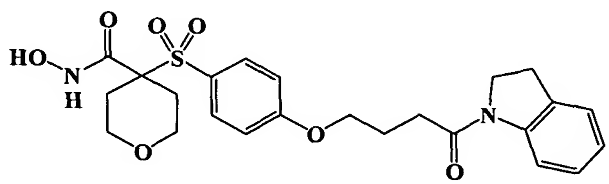


IIA-47



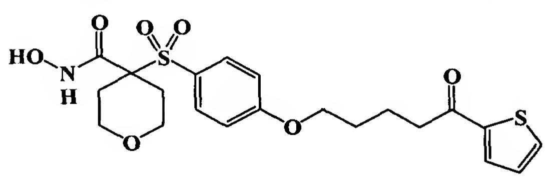
IIA-48

[119] In other preferred embodiments, E^5 is optionally-substituted heterocyclyl. In one such embodiment, E^5 is optionally-substituted thiophenyl. Such compounds include, for example:

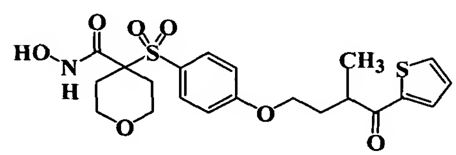


IIA-49

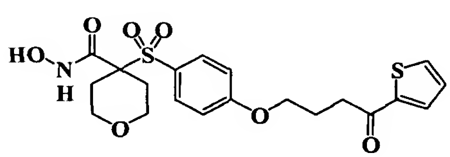
Other such compounds include, for example:



IIA-50



IIA-51



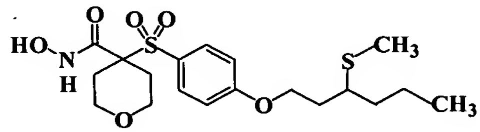
IIA-52

Preferred Embodiment No. 1-b: E^3 is -S-

[120] In some embodiments, E^3 is -S-.

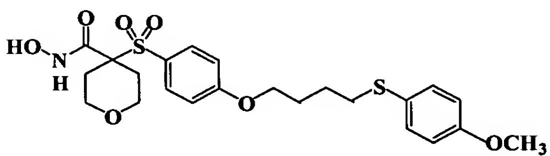
[121] In some such embodiments, E^5 is -H, -OH, C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, or C_1-C_8-alkoxy-C_1-C_8-alkyl. The C_1-C_8-alkyl,

C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. Such compounds include, for example:

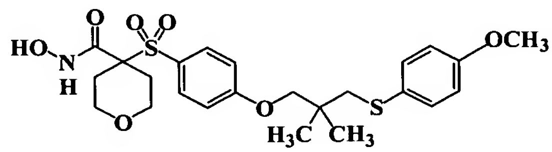


IIB-1

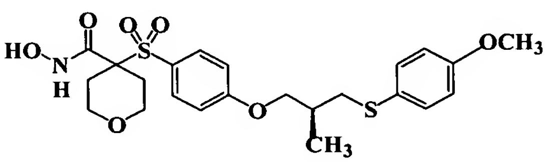
[122] In some preferred embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



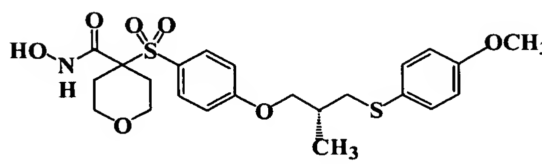
IIB-2



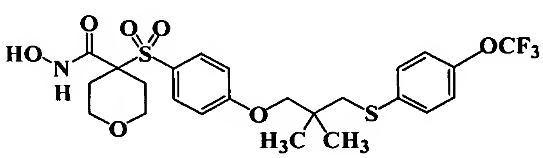
IIB-3



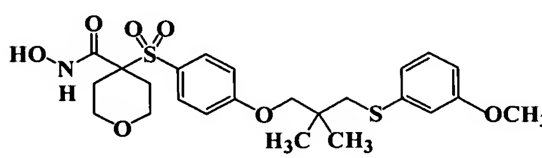
IIB-4



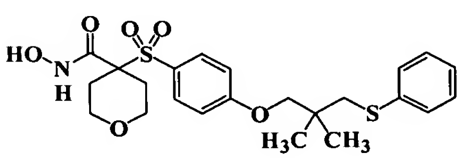
IIB-5



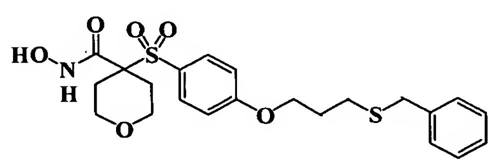
IIB-6



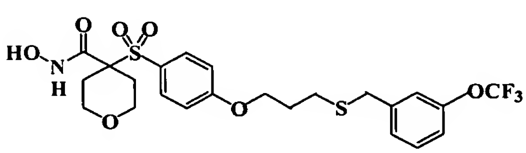
IIB-7



IIB-8

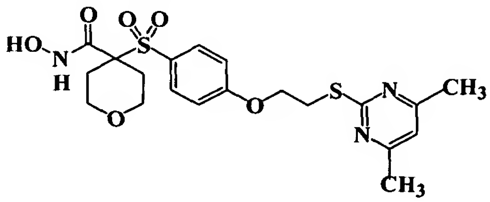


IIB-9

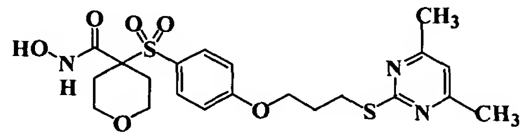


IIB-10

[123] In some preferred embodiments, E^5 is optionally-substituted heterocyclyl. In one such embodiment, E^5 is optionally-substituted pyrimidinyl. Such compounds include, for example:

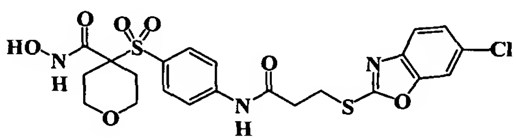


IIB-11

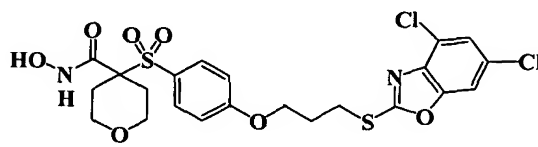


IIB-12

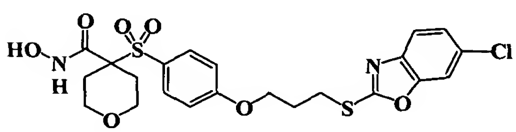
In another such embodiment, E^5 is optionally-substituted 2-fused-ring heterocyclyl. In some preferred embodiments, E^5 is optionally-substituted benzoxazolyl or optionally-substituted benzothiazolyl. Such compounds include, for example:



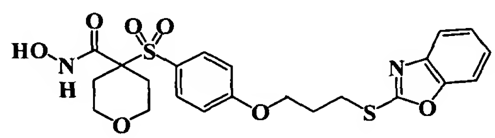
IIB-13



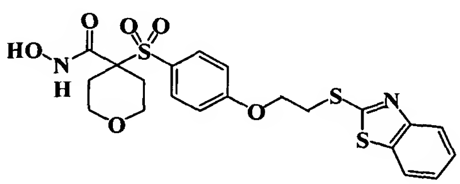
IIB-14



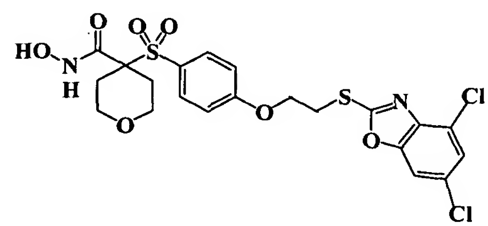
IIB-15



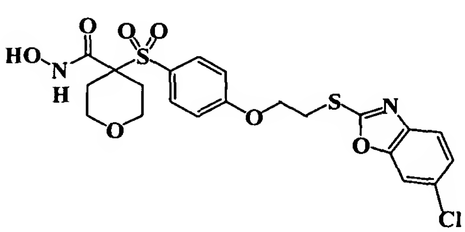
IIB-16



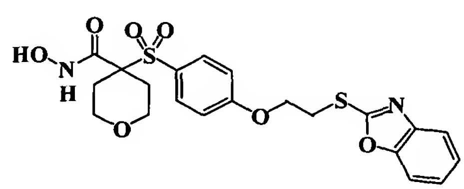
IIB-17



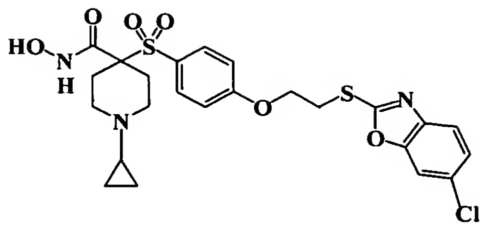
IIB-18



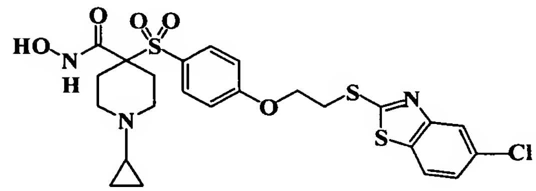
IIB-19



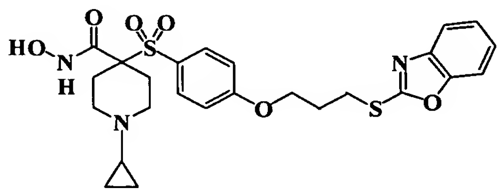
IIB-20



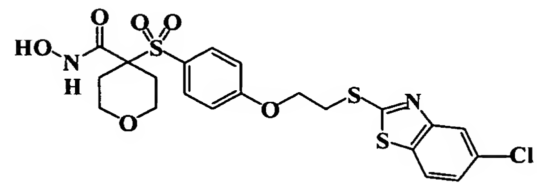
IIB-21



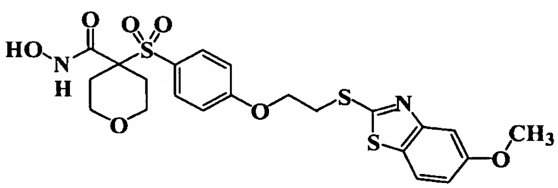
IIB-22



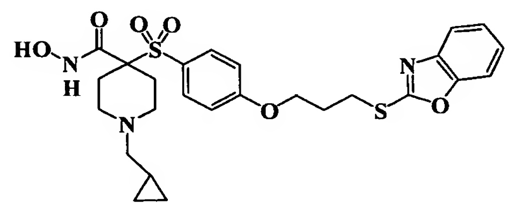
IIB-23



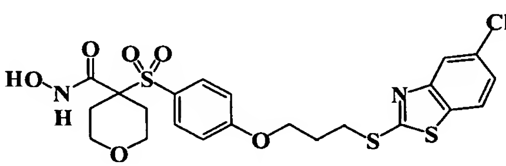
IIB-24



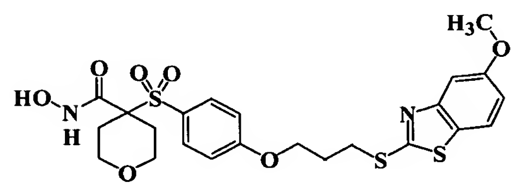
IIB-25



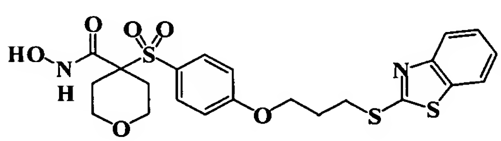
IIB-26



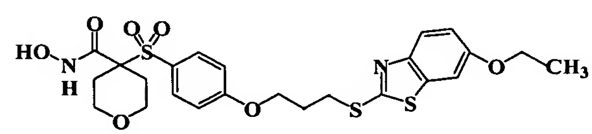
IIB-27



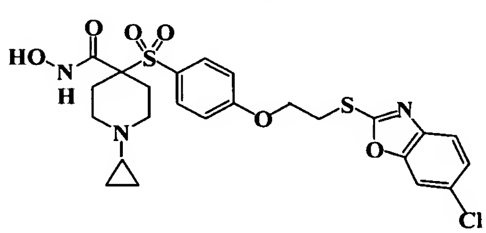
IIB-28



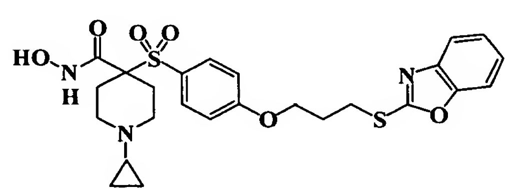
IIB-29



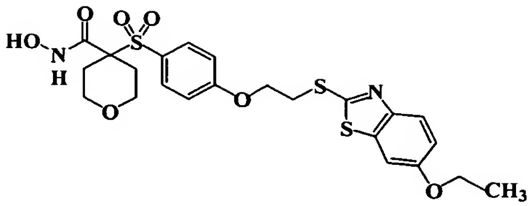
IIB-30



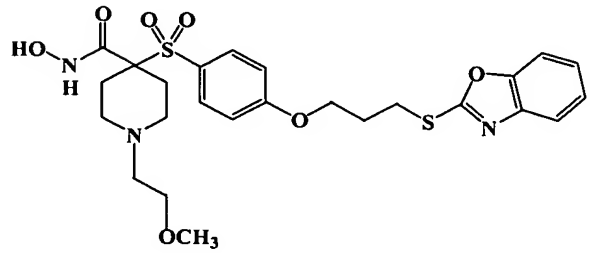
IIB-31



IIB-32

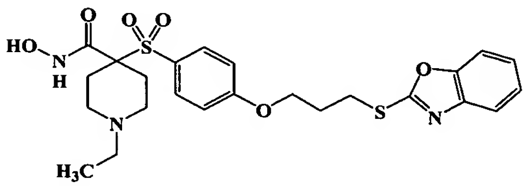


IIB-33

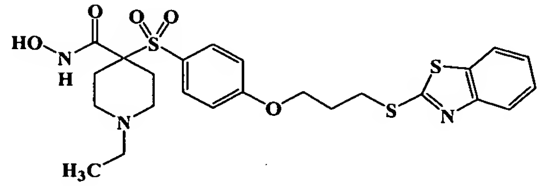


IIB-34

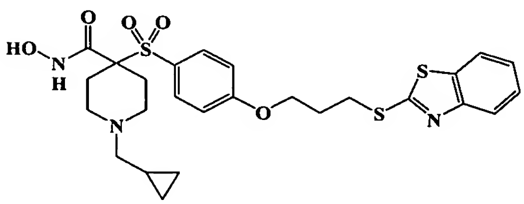
Other such compounds include, for example:



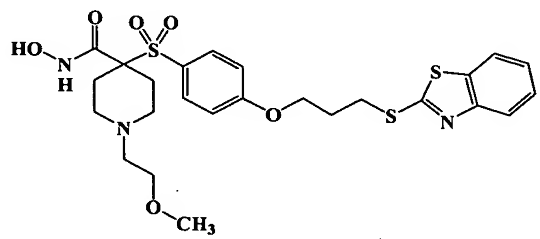
IIB-35



IIB-36



IIB-37

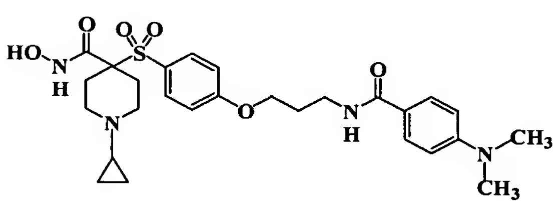


IIB-38

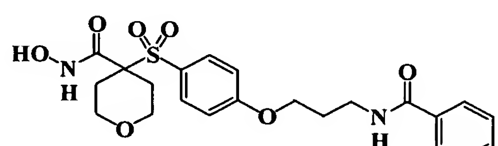
Preferred Embodiment No. 1-c: E^3 is -N(R^4)-C(O)-

[124] In some embodiments, E^3 is -N(R^4)-C(O)-.

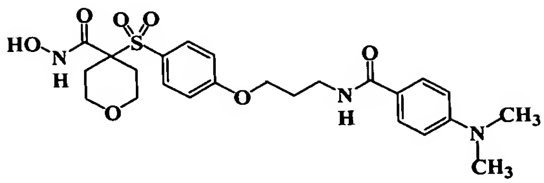
[125] In some such embodiments, E^5 is optionally-substituted carbocyclyl. In some preferred embodiments, E^5 is optionally-substituted phenyl. Such compounds include, for example:



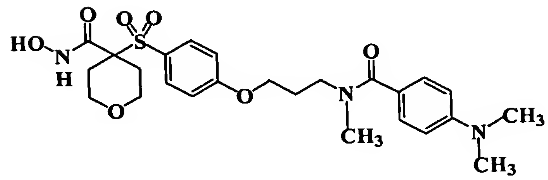
IIC-1



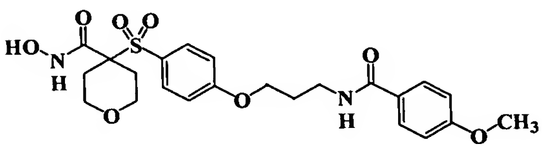
IIC-2



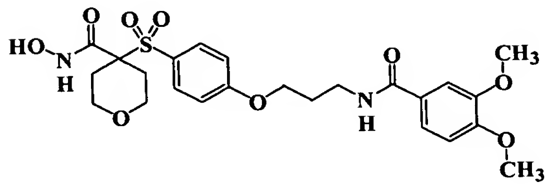
IIC-3



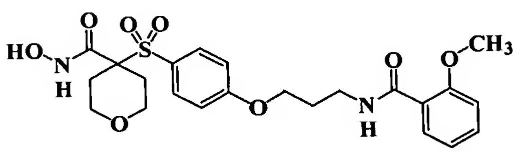
IIC-4



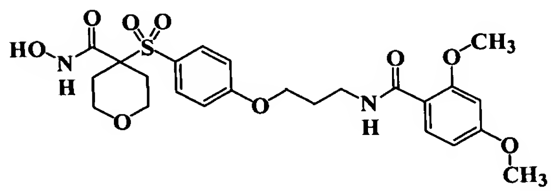
IIC-5



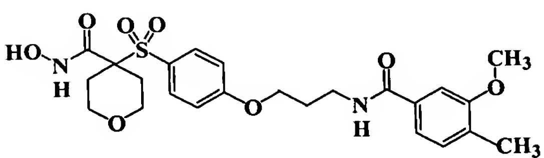
IIC-6



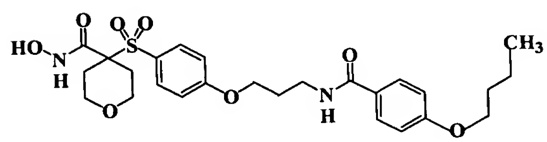
IIC-7



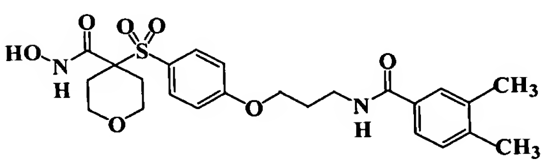
IIC-8



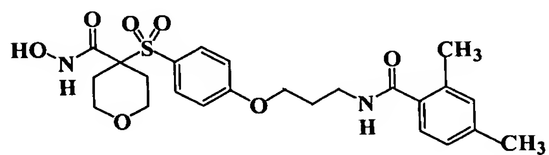
IIC-9



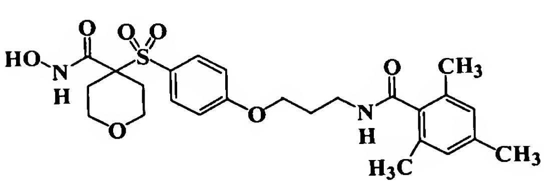
IIC-10



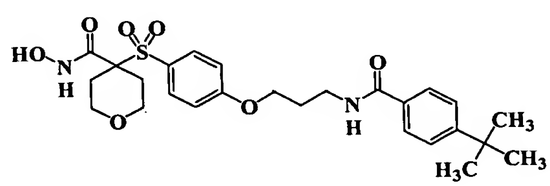
IIC-11



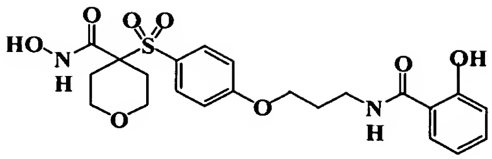
IIC-12



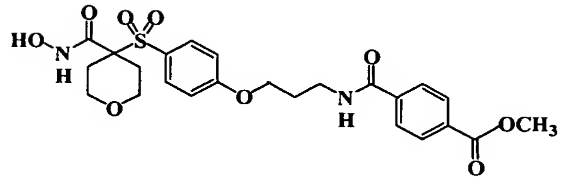
IIC-13



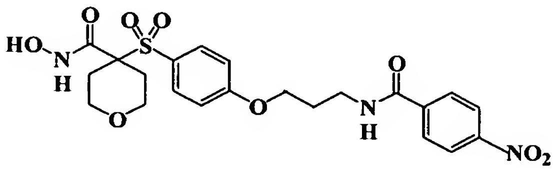
IIC-14



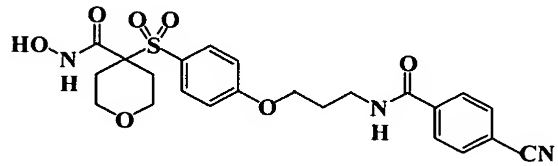
IIC-15



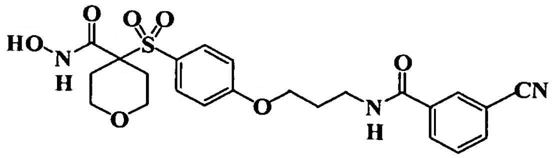
IIC-16



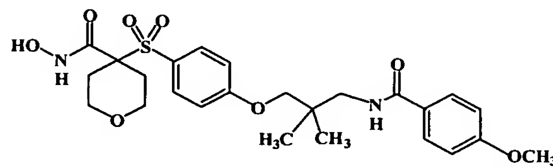
IIC-17



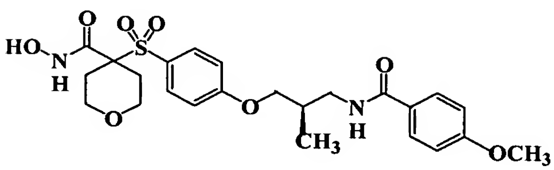
IIC-18



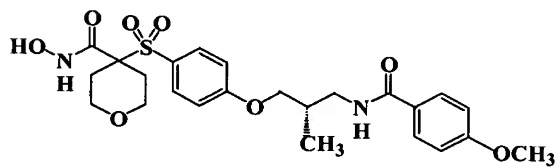
IIC-19



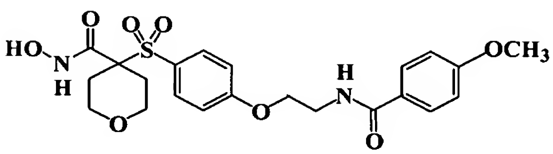
IIC-20



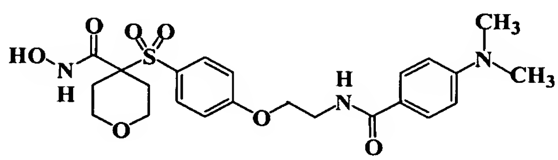
IIC-21



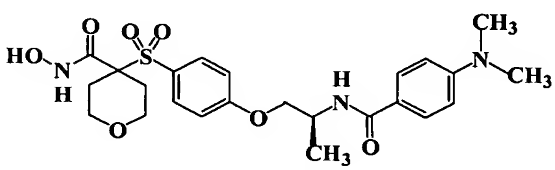
IIC-22



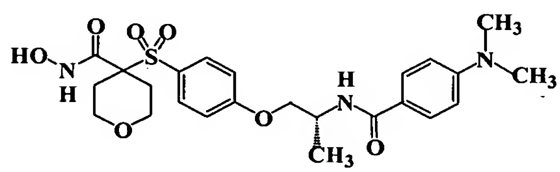
IIC-23



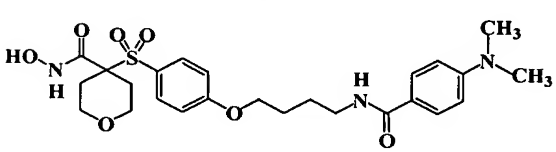
IIC-24



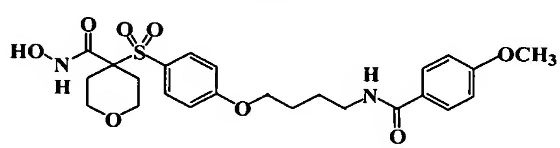
IIC-25



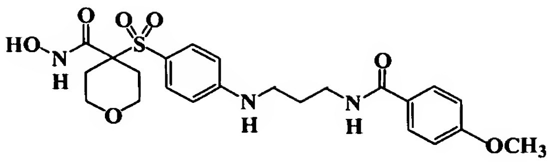
IIC-26



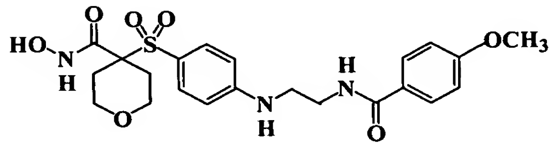
IIC-27



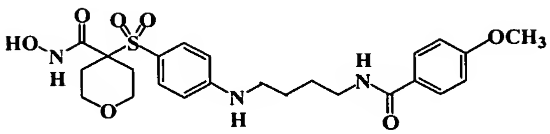
IIC-28



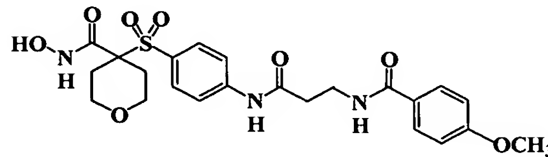
IIC-29



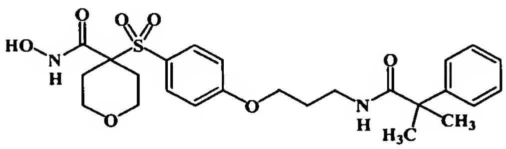
IIC-30



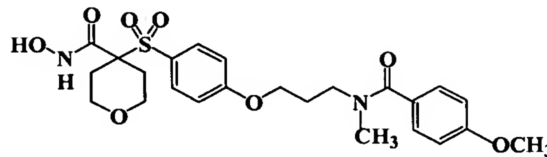
IIC-31



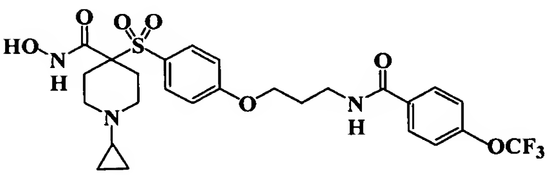
IIC-32



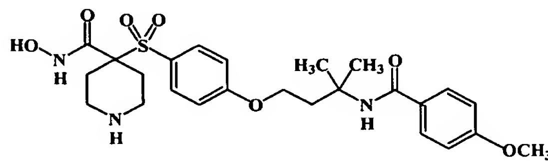
IIC-33



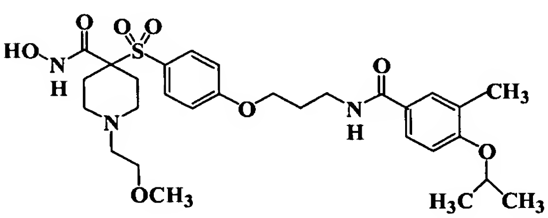
IIC-34



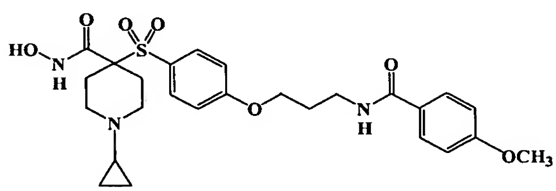
IIC-35



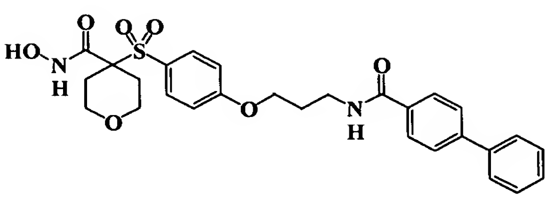
IIC-36



IIC-37

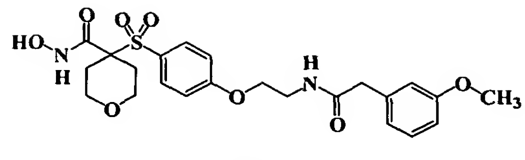


IIC-38

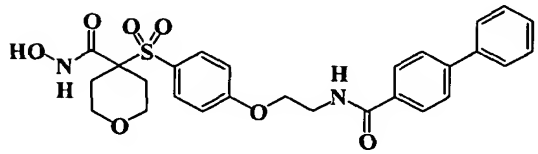


IIC-39

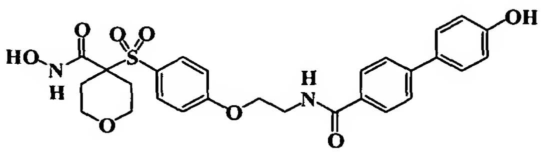
Other such compounds include, for example:



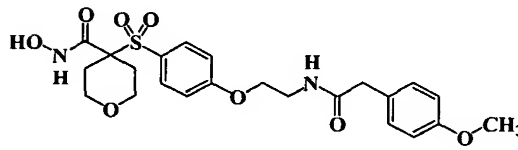
IIC-40



IIC-41

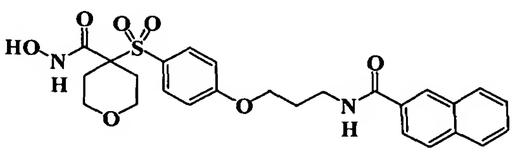


IIC-42

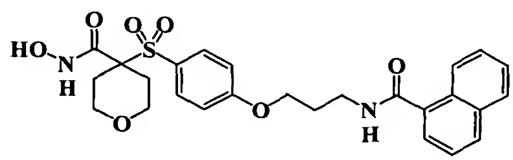


IIC-43

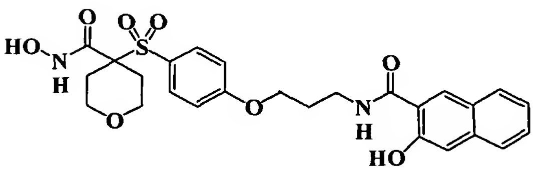
[126] In some preferred embodiments, E^5 is optionally-substituted naphthalenyl. Such compounds include, for example:



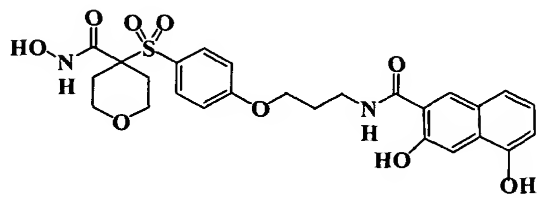
IIC-44



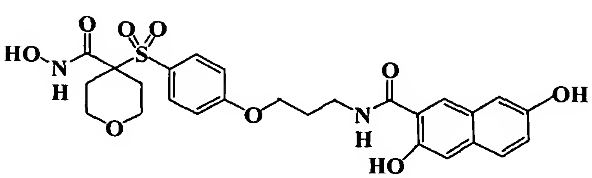
IIC-45



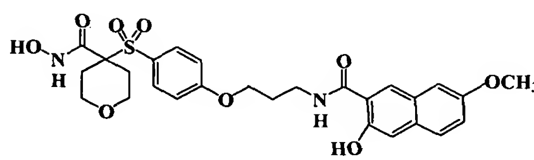
IIC-46



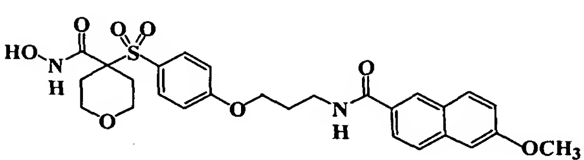
IIC-47



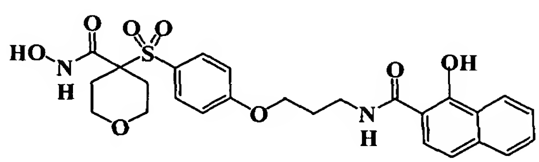
IIC-48



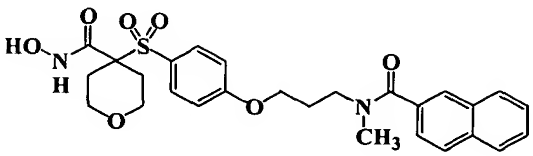
IIC-49



IIC-50

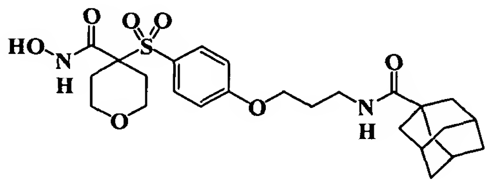


IIC-51



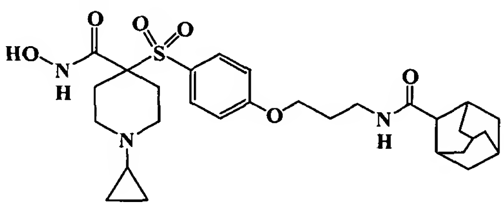
IIC-52

[127] In some preferred embodiments, E^5 is optionally-substituted cycloalkyl. Such compounds include, for example, fused-ring cycloalkyls. These compounds include, for example:

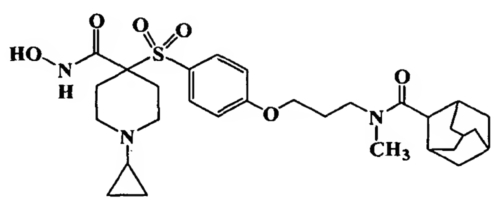


IIC-53

These compounds also include, for example:

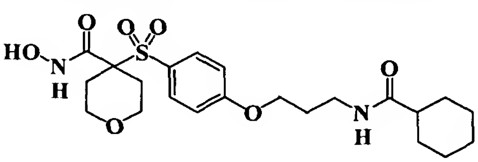


IIC-54

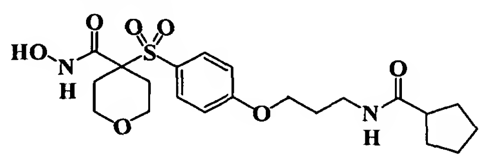


IIC-55

[128] In some preferred embodiments, E^5 is optionally-substituted C_5-C_6-cycloalkyl. These compounds include, for example:

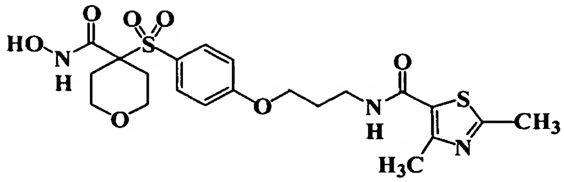


IIC-56

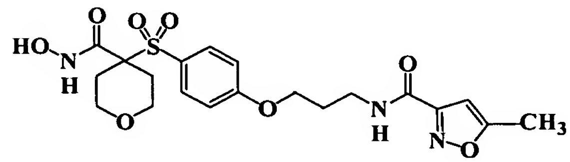


IIC-57

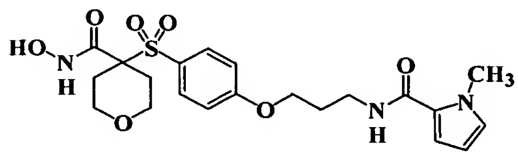
[129] In some preferred embodiments, E^5 is optionally-substituted heterocyclyl. In one such embodiment, E^5 is an optionally-substituted heterocyclyl selected from the group consisting of pyridinyl, pyrrolyl, isopyrrolyl, oxazolyl, isoxazole, thiazolyl, furanyl, and morpholinyl. In another such embodiment, E^5 is an optionally-substituted heterocyclyl selected from the group consisting of tetrazolyl, imidazolyl, and thienyl. Compounds of these embodiments include, for example:



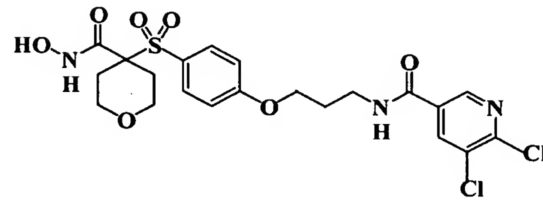
IIC-58



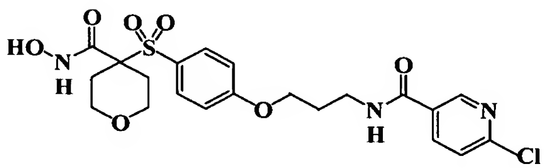
IIC-59



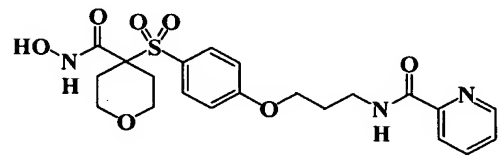
IIC-60



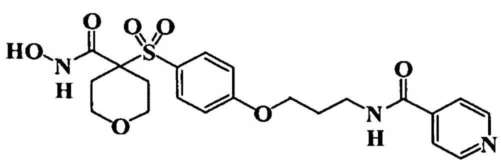
IIC-61



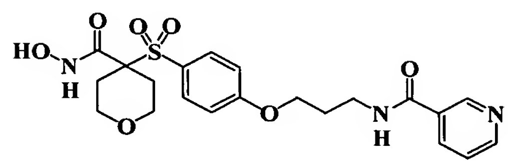
IIC-62



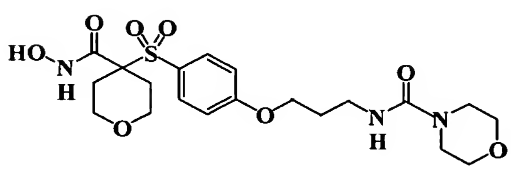
IIC-63



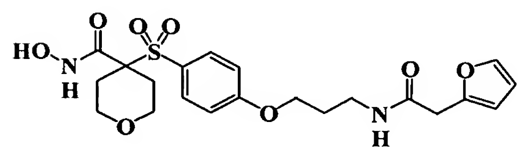
IIC-64



IIC-65

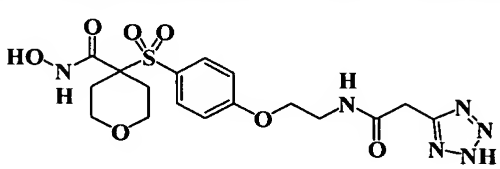


IIC-66

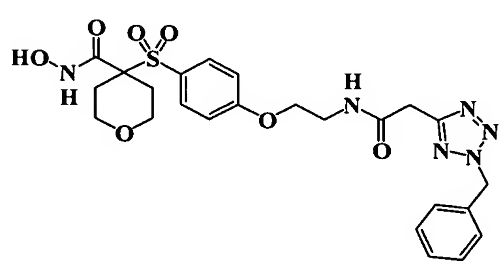


IIC-67

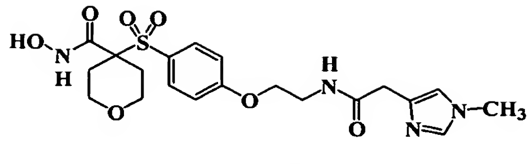
Such compounds also include, for example:



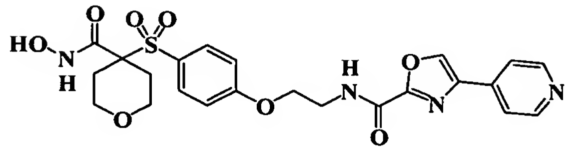
IIC-68



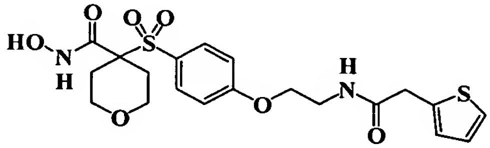
IIC-69



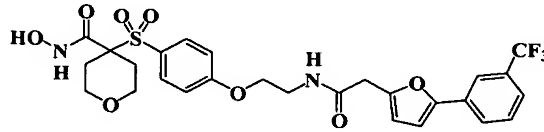
IIC-70



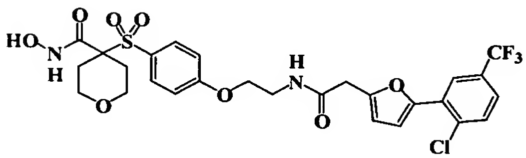
IIC-71



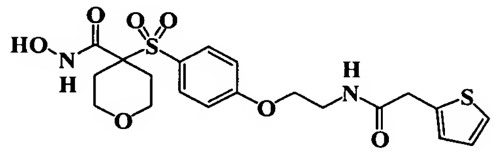
IIC-72



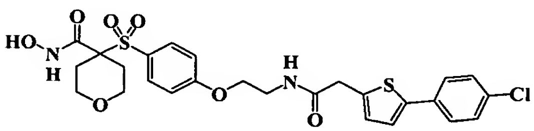
IIC-73



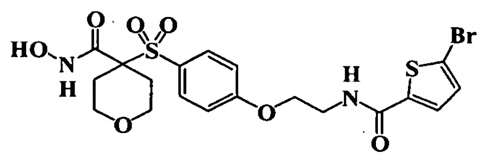
IIC-74



IIC-75

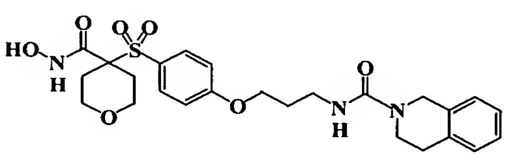


IIC-76

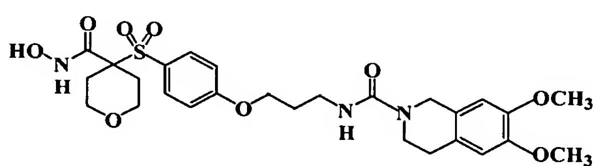


IIC-77

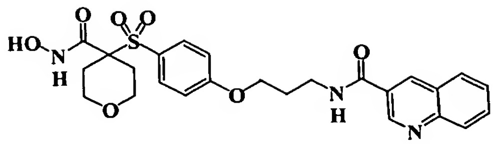
[130] In some preferred embodiments, E^5 is optionally-substituted 2-fused-ring heterocyclyl. In some more preferred embodiments, E^5 is an optionally-substituted heterocyclyl selected from the group consisting of benzazinyl, benzofuranyl, tetrahydroisoquinolinyl or pyridofuranyl. In some other more preferred embodiments, E^5 is an optionally-substituted heterocyclyl selected from the group consisting of indolyl, benzoxazolyl, benzothienyl, and benzothiazolyl. Compounds of such embodiments include, for example:



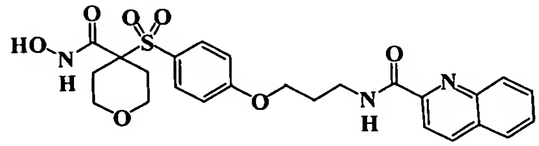
IIC-78



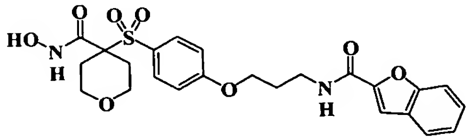
IIC-79



IIC-80

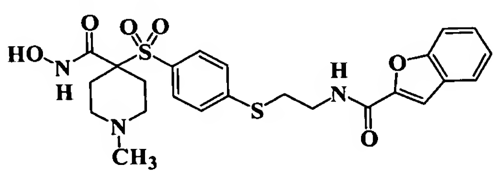


IIC-81

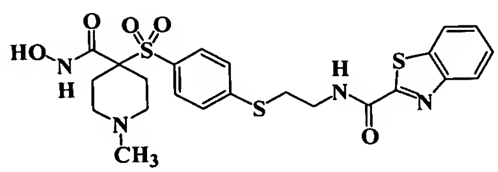


IIC-82

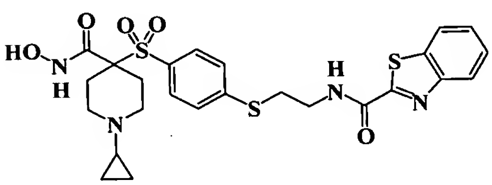
Other such compounds include, for example:



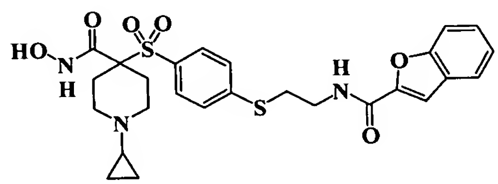
IIC-83



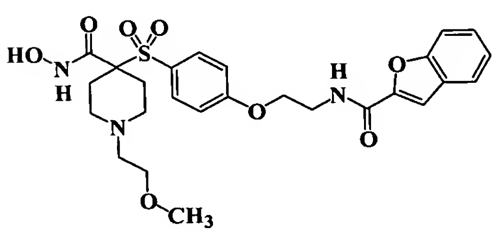
IIC-84



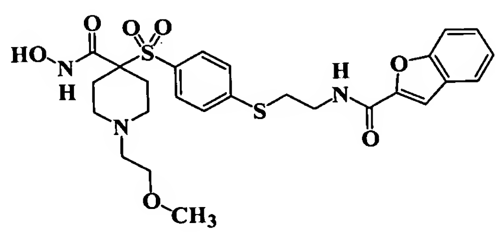
IIC-85



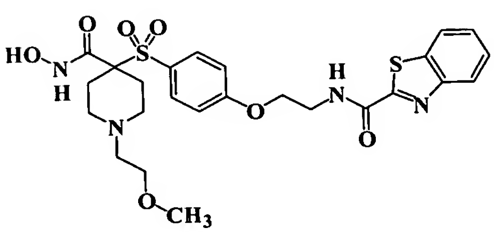
IIC-86



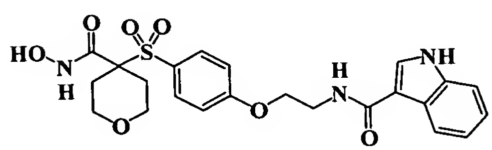
IIC-87



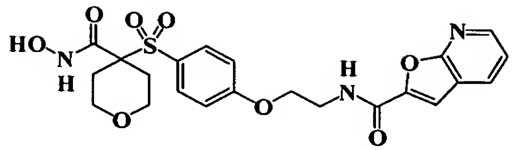
IIC-88



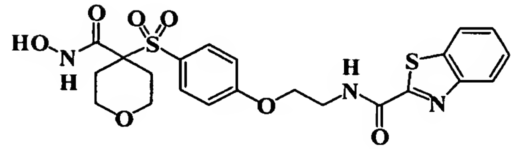
IIC-89



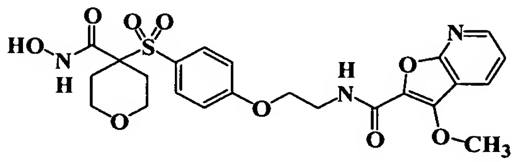
IIC-90



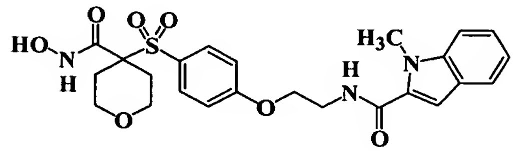
IIC-91



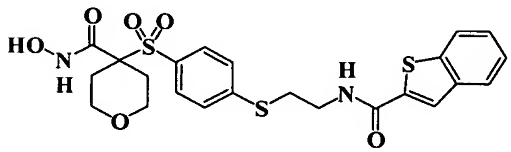
IIC-92



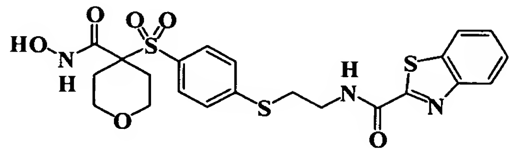
IIC-93



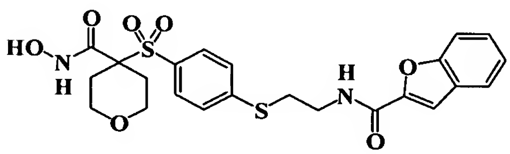
IIC-94



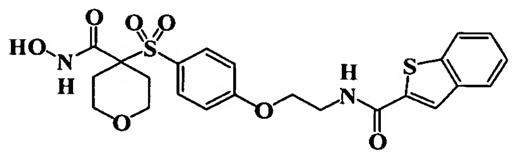
IIC-95



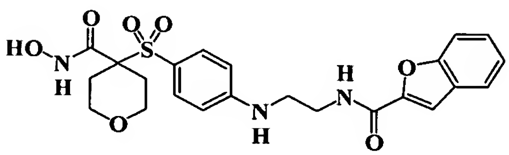
IIC-96



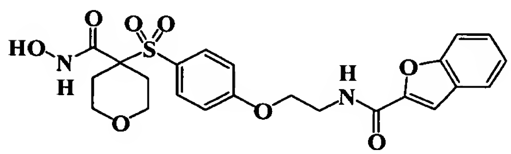
IIC-97



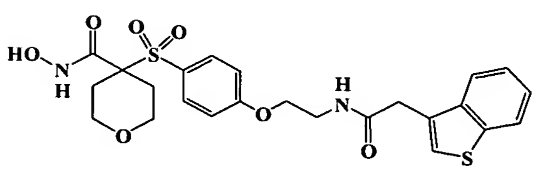
IIC-98



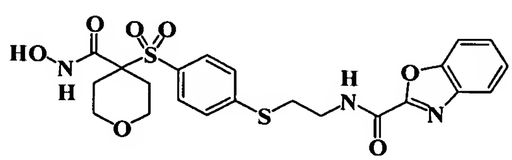
IIC-99



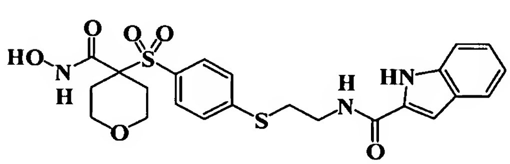
IIC-100



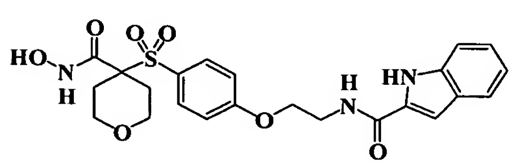
IIC-101



IIC-102



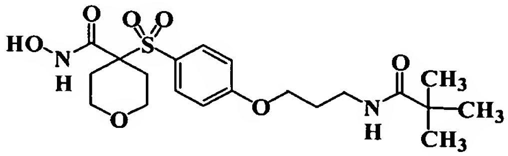
IIC-103



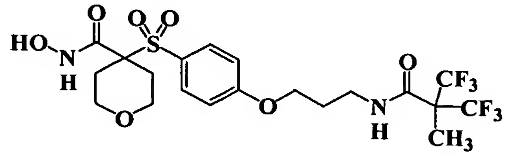
IIC-104

[131] In some preferred embodiments, E^5 is -OH, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, or C_1-C_6-alkoxy-C_1-C_6-alkyl. Except where the member is

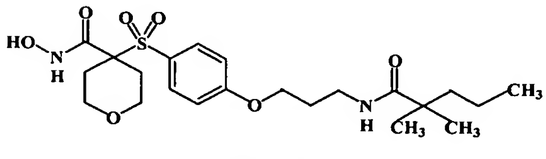
-OH, any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. Such compounds include, for example:



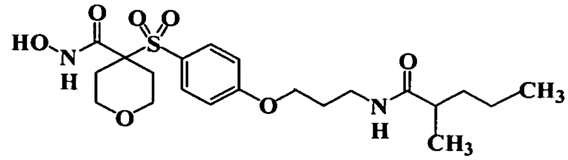
IIC-105



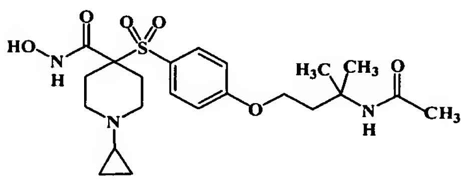
IIC-106



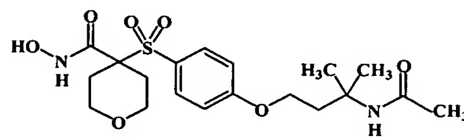
IIC-107



IIC-108



IIC-109



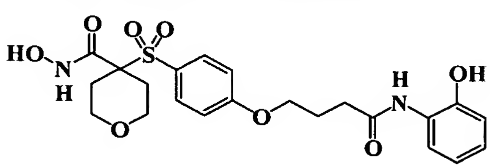
IIC-110

Preferred Embodiment No. 1-d: E^3 is -C(O)-N(R^4)-

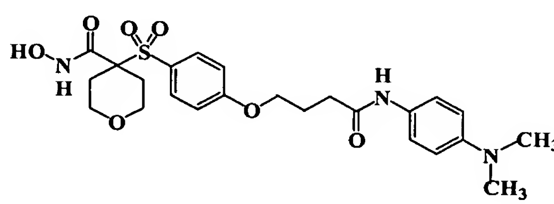
[132] In some embodiments, E^3 is -C(O)-N(R^4)-.

[133] In some such embodiments, for example, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl.

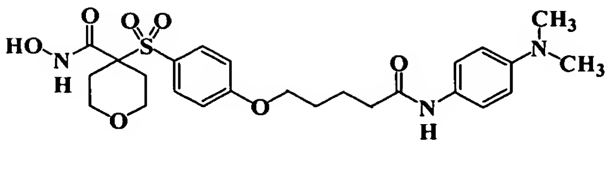
[134] In some preferred embodiments, E^5 is optionally-substituted phenyl. Such compounds include, for example:



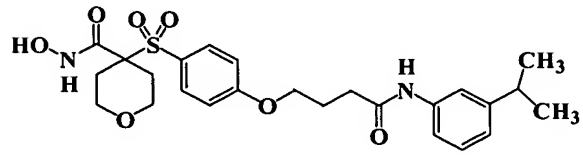
IID-1



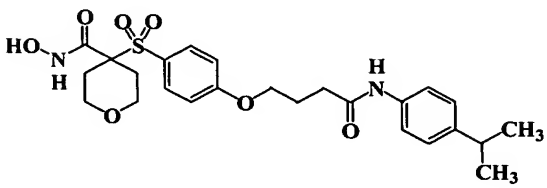
IID-2



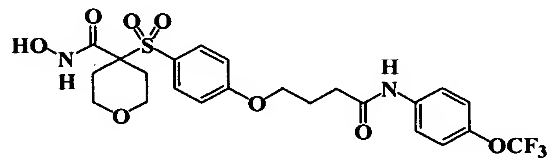
IID-3



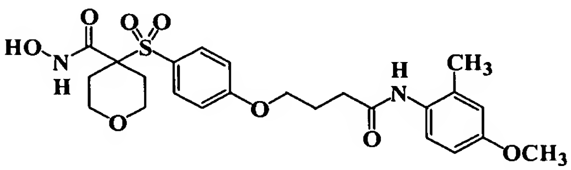
IID-4



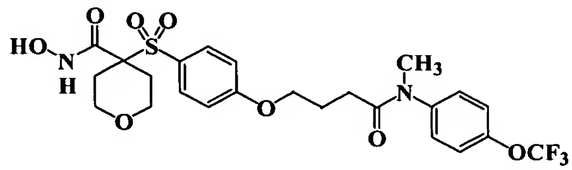
IID-5



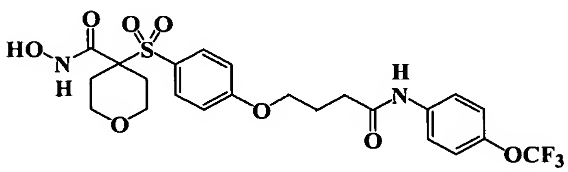
IID-6



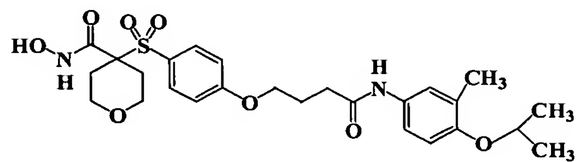
IID-7



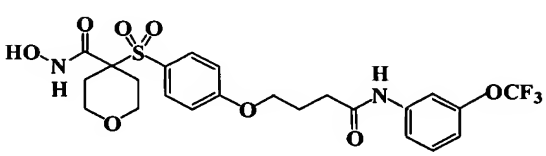
IID-8



IID-9

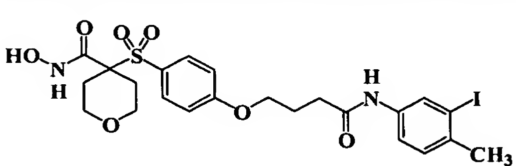


IID-10

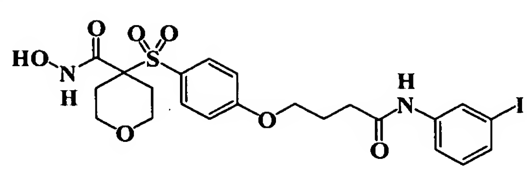


IID-11

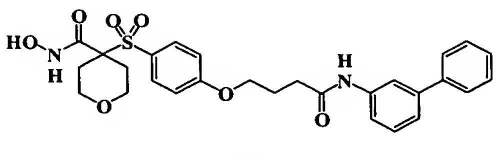
Other such compounds include, for example:



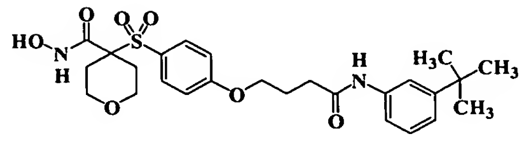
IID-12



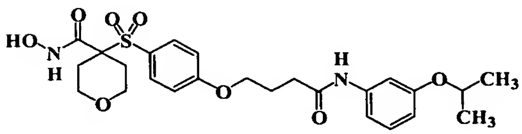
IID-13



IID-14

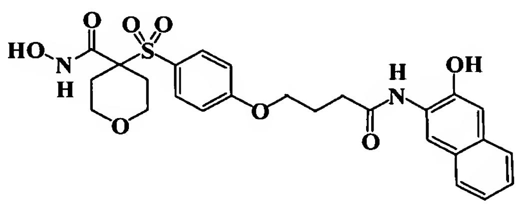


IID-15



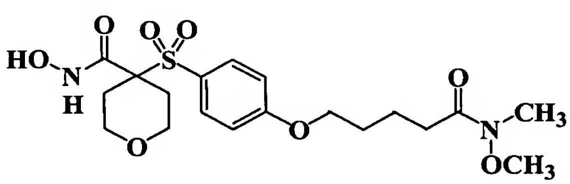
IID-16

[135] In some preferred embodiments, E^5 is optionally-substituted naphthalenyl. These compounds include, for example:



IID-17

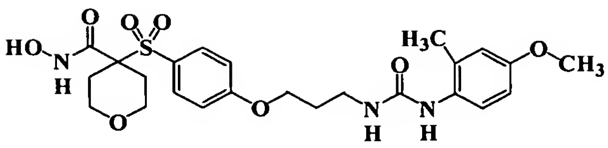
[136] In some preferred embodiments, E^5 is -OH, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, or C_1-C_6-alkoxy-C_1-C_6-alkyl. Except where the member is -OH, any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. Such compounds include, for example:



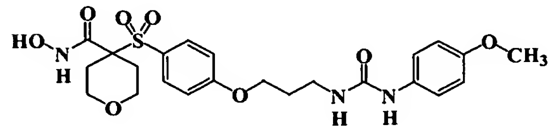
IID-18

Preferred Embodiment No. 1-e: E^3 is $-N(R^4)-C(O)-N(R^5)-$

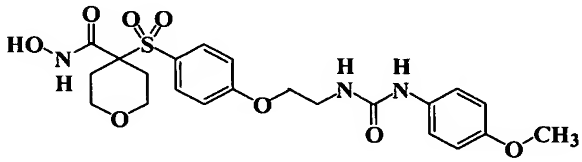
[137] In some embodiments, E^3 is $-N(R^4)-C(O)-N(R^5)-$. In some such embodiments, for example, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



IIE-1



IIE-2

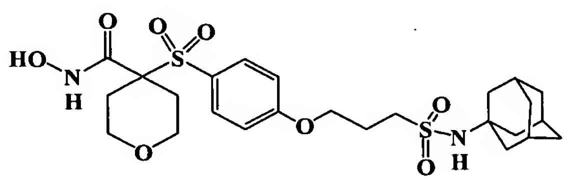


IIE-3

Preferred Embodiment No. 1-f: E^3 is $-S(O)_2-N(R^4)-$

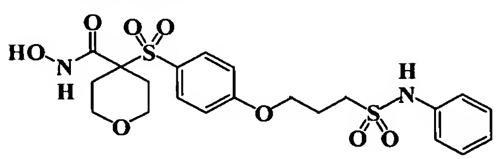
[138] In some embodiments, E^3 is $-S(O)_2-N(R^4)-$.

[139] In some such embodiments, E^5 is optionally-substituted carbocyclyl. The carbocyclyl may be, for example, cycloalkyl. Such compounds include, for example:

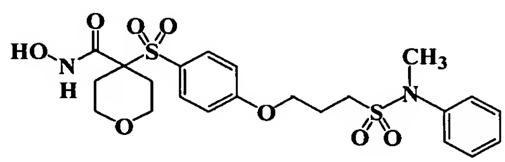


IIF-1

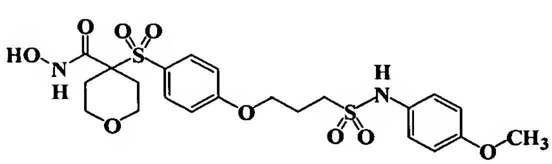
In some preferred embodiments, the carbocyclyl is aryl (preferably phenyl). Such compounds include, for example:



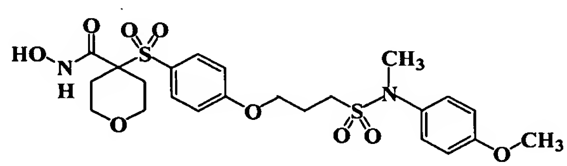
IIF-2



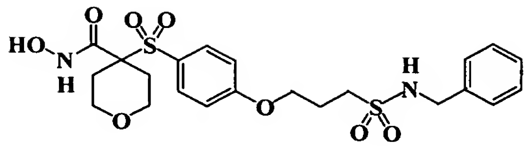
IIF-3



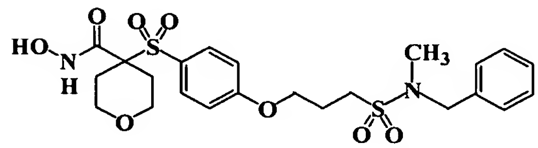
IIF-4



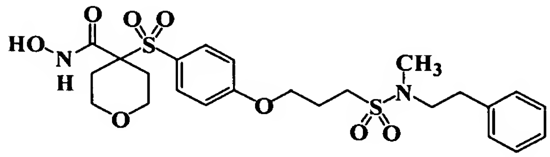
IIF-5



IIF-6

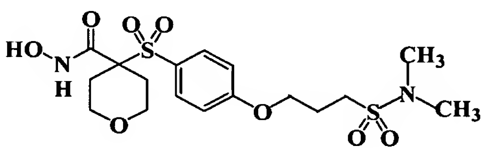


IIF-7

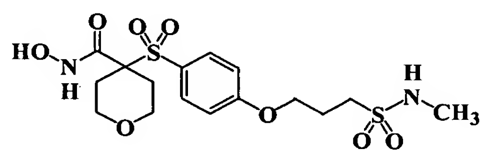


IIF-8

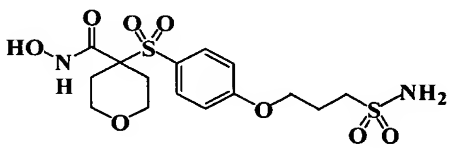
[140] In some preferred embodiments, E^5 is -H, -OH, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, or C_1-C_6-alkoxy-C_1-C_6-alkyl. Except where the member is -H or -OH, any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. Such compounds include, for example:



IIF-9



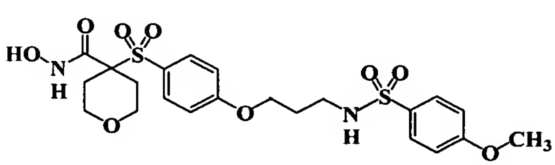
IIF-10



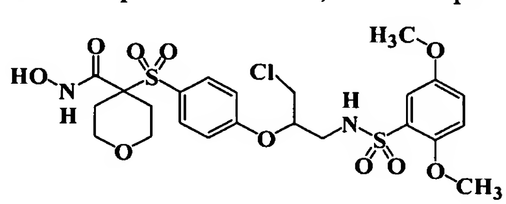
IIF-11

Preferred Embodiment No. 1-g: E^3 is $-N(R^4)-S(O)_2-$

[141] In some embodiments, E^3 is $-N(R^4)-S(O)_2-$. In some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:

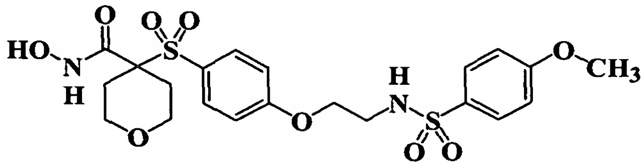


IIG-1



IIG-2

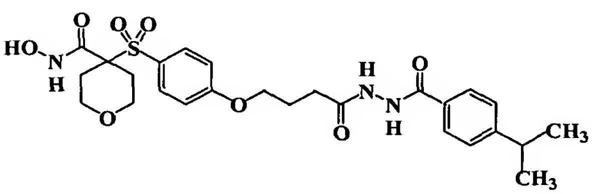
Other such compounds include, for example:



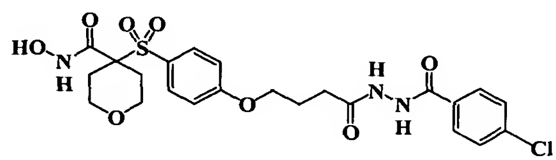
IIG-3

Preferred Embodiment No. 1-h: E^3 is -C(O)-N(R^4)-N(R^5)-C(O)-

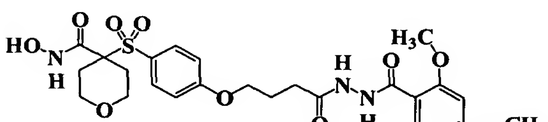
[142] In some embodiments, E^3 is -C(O)-N(R^4)-N(R^5)-C(O)-. In some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



IIH-1



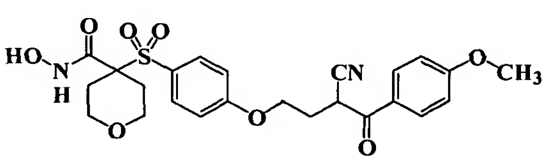
IIH-2



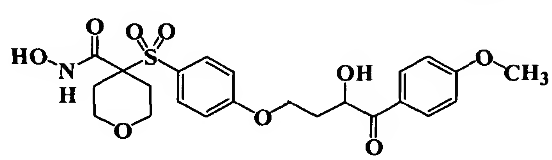
IIH-3

Preferred Embodiment No. 1-i: E^3 is -C(R^4)(R^6)-C(O)-

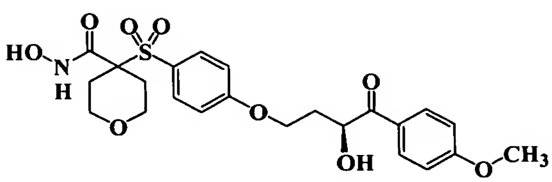
[143] In some embodiments, E^3 is -C(R^4)(R^6)-C(O)-. In some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



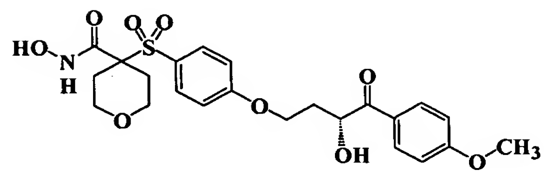
III-1



III-2



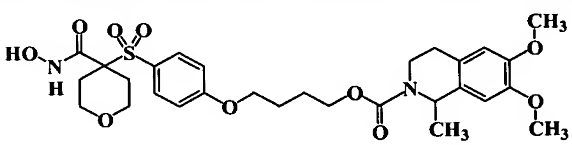
III-3



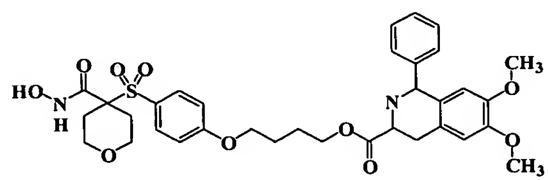
III-4

Preferred Embodiment No. 1-j: E^3 is -O-C(O)-

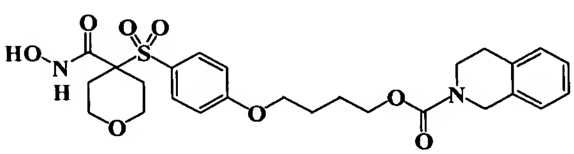
[144] In some embodiments, E^3 is *-O-C(O)-*. In some such embodiments, E^5 is optionally-substituted heterocyclyl. In some preferred embodiments, E^5 is an optionally-substituted 2-fused-ring heterocyclyl. In some embodiments, for example, E^5 is optionally-substituted tetrahydroisoquinolinyl . Such compounds include, for example:



IIJ-1



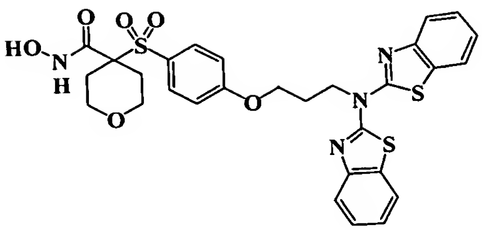
IIJ-2



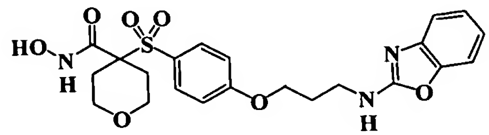
IIJ-3

Preferred Embodiment No. 1-k: E^3 is -N(R^4)-

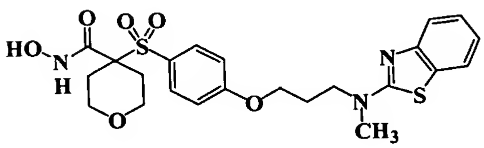
[145] In some embodiments, E^3 is *-N(R^4)-*. In some such embodiments, E^5 is optionally-substituted heterocyclyl. In some preferred embodiments, E^5 is optionally-substituted 2-fused-ring heterocyclyl. In some embodiments, for example, E^5 is optionally-substituted benzoxazolyl, benzothiazolyl, or benzimidazolyl. Such compounds include, for example:



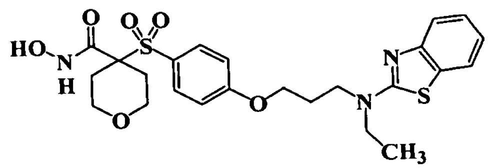
IIK-1



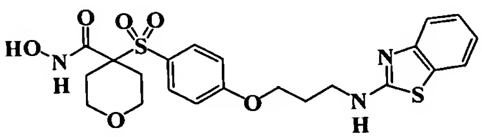
IIK-2



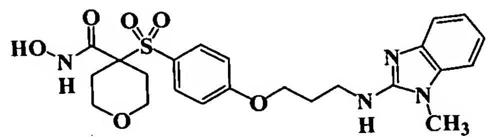
IIK-3



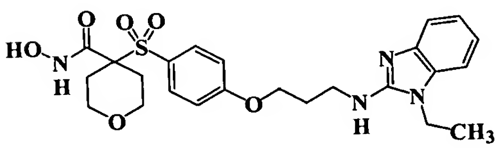
IIK-4



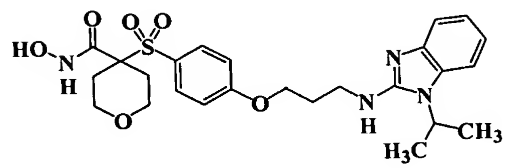
IIK-5



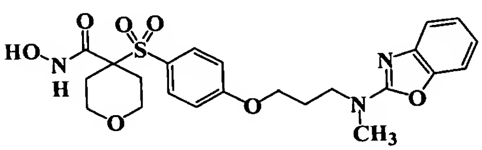
IIK-6



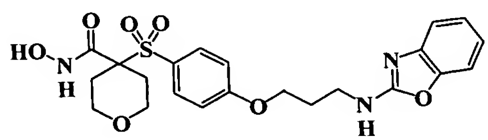
IIK-7



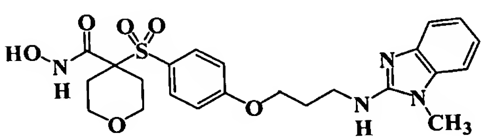
IIK-8



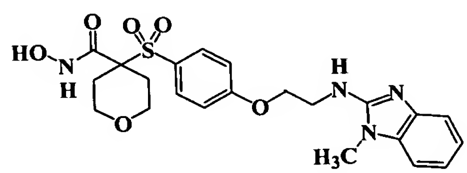
IIK-9



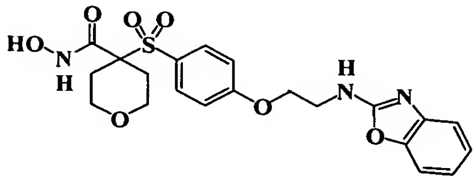
IIK-10



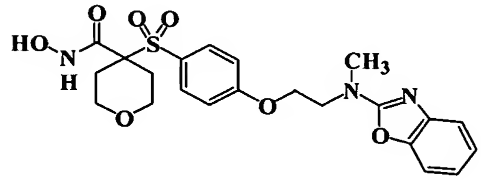
IIK-11



IIK-12



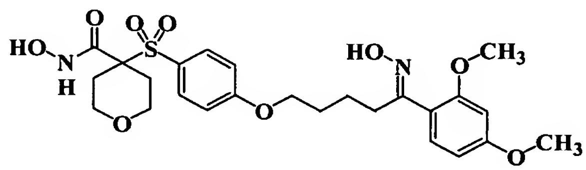
IIK-13



IIK-14

Preferred Embodiment No. 1-l: E^3 is -C(NR^3)-

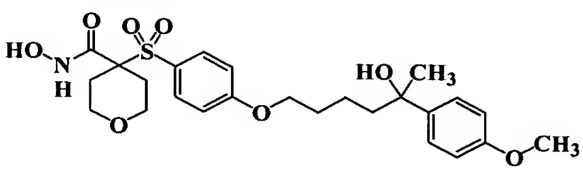
[146] In some embodiments, E^3 is *-C(NR^3)-*. In some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



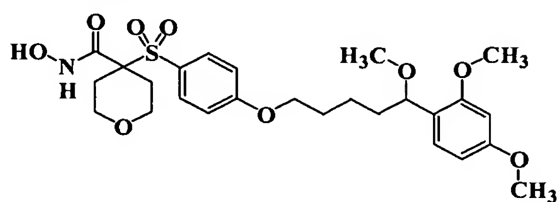
IIL-1

Preferred Embodiment No. 1-m: E^3 is -C(R^7)(R^8)-

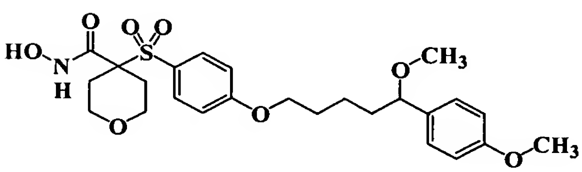
[147] In some embodiments, E^3 is *-C(R^7)(R^8)-*. In some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



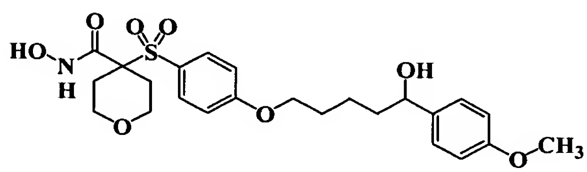
IIM-1



IIM-2



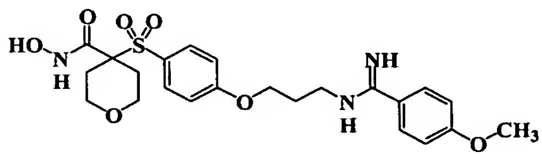
IIM-3



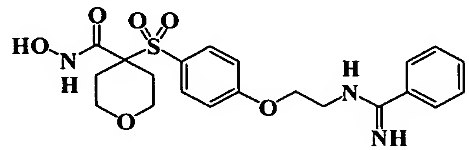
IIM-4

Preferred Embodiment No. 1-n: E^3 is -N(R^4)-C(NR^3)-

[148] In some embodiments, E^3 is -N(R^4)-C(NR^3)-. In some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



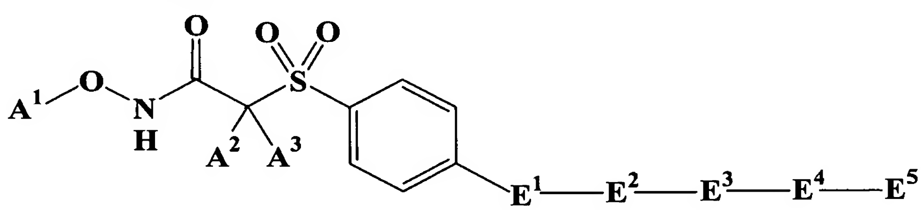
IIN-1



IIN-2

Preferred Embodiment No. 2

[149] In some embodiments of this invention, the compound has a structure corresponding to Formula III:



III

[150] A^1, A^2, and A^3 are as defined above for Formula I.

[151] E^1 is -O-, -S(O)$_2$-, -S(O)-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-. E^1 alternatively may be -S-.

[152] E^2 forms a link of at least 2 carbon atoms between E^1 and E^3. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[153] In some preferred embodiments, E^2 is C_2-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[154] In some preferred embodiments, E^2 is C_2-C_6-alkyl optionally substituted with one or more halogen.

[155] In some preferred embodiments, E^2 is C_2-C_5-alkyl optionally substituted with one or more halogen.

[156] In some preferred embodiments, E^2 is C_2-C_5-alkyl.

[157] In some preferred embodiments, E^2 is $-(CH_2)_m-$, wherein m is from 2 to 5.

[158] E^3 is carbocyclyl or heterocyclyl. This carbocyclyl and heterocyclyl have 5 or 6 ring members and optionally are substituted.

[159] In some preferred embodiments, E^3 is carbocyclyl or heterocyclyl wherein the carbocyclyl and heterocyclyl have 5 or 6 ring members and optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, keto, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the substituent is halogen, -OH, or keto, any of these substituents optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, C_1-C_8-alkylthio, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, halo-C_1-C_8-alkylthio, and halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl.

[160] In some preferred embodiments, E^3 is carbocyclyl or heterocyclyl wherein the carbocyclyl and heterocyclyl have 5 or 6 ring members and optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, keto, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the substituent is halogen, -OH, or keto, any substituent of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylthio, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and halo-C_1-C_6-alkylthio.

[161] E^4 is a bond, alkyl, alkenyl, -O-, or $-N(R^3)-$. The alkyl and alkenyl optionally are substituted.

[162] In some preferred embodiments, E^4 is a bond, -O-, $-N(R^3)-$, C_1-C_{20}-alkyl, or C_2-C_{20}-alkenyl. The C_1-C_{20}-alkyl and C_2-C_{20}-alkenyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen and carbocyclyl optionally substituted with one or more substituents independently selected

from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, halocarbocyclyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, and halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl.

[163] In some preferred embodiments, E^4 is a bond, -O-, -N(R^3)-, C_1-C_3-alkyl, or C_2-C_3-alkenyl. The C_1-C_3-alkyl and C_2-C_3-alkenyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen and carbocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[164] In some preferred embodiments, E^4 is a bond, -O-, -N(R^3)-, C_1-C_3-alkyl, or C_2-C_3-alkenyl.

[165] In some preferred embodiments, E^4 is a bond.

[166] E^5 is carbocyclyl or heterocyclyl. The carbocyclyl and heterocyclyl optionally are substituted. In some preferred embodiments, the carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, -N(R^6)(R^7), -C(O)(R^8), -S-R^6, -S(O)$_2$-R^6, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl. The carbocyclyl and heterocyclyl also optionally are substituted with one or more substituents independently selected from the group consisting of C_2-C_8-alkenyl and C_2-C_8-alkynyl.

[167] In some preferred embodiments, E^5 is pyridinyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -N(R^6)(R^7), -C(O)(R^8), -S-R^6, -S(O)$_2$-R^6, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl. The pyridinyl also is optionally substituted with

one or more substituents independently selected from the group consisting of C_2-C_6-alkenyl and C_2-C_6-alkynyl.

[168] In some preferred embodiments, E^5 is piperidinyl, piperazinyl, imidazolyl, furanyl, thienyl, pyrimidyl, benzodioxolyl, benzodioxanyl, benzofuryl, or benzothienyl. Such substituent optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^6)(R^7)$, $-C(O)(R^8)$, $-S-R^6$, $-S(O)_2-R^6$, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl. Such substituent also optionally is substituted with one or more substituents independently selected from the group consisting of C_2-C_6-alkenyl and C_2-C_6-alkynyl.

[169] In some preferred embodiments, E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^6)(R^7)$, $-C(O)(R^8)$, $-S-R^6$, $-S(O)_2-R^6$, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl. The phenyl also is optionally substituted with one or more substituents independently selected from the group consisting of C_2-C_6-alkenyl and C_2-C_6-alkynyl.

[170] In some preferred embodiments, E^5 is naphthalenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^6)(R^7)$, $-C(O)(R^8)$, $-S-R^6$, $-S(O)_2-R^6$, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl. The naphthalenyl also is optionally substituted with one or more substituents independently selected from the group consisting of C_2-C_6-alkenyl and C_2-C_6-alkynyl.

[171] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

[172] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl.

[173] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[174] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_6-alkyl.

[175] R^3 is -H or alkyl. The alkyl optionally is substituted.

[176] In some preferred embodiments, R^3 is -H, C_1-C_8-alkyl, or halo-C_1-C_8-alkyl.

[177] In some preferred embodiments, R^3 is -H, C_1-C_6-alkyl, or halo-C_1-C_6-alkyl.

[178] In some preferred embodiments, R^3 is -H or C_1-C_8-alkyl.

[179] R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halocarbocyclyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, haloheterocyclyl, and halogen-substituted heterocyclyl-C_1-C_8-alkyl.

[180] In some preferred embodiments, R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[181] R^8 is -H, C_1-C_8-alkyl, -O-R^9, -N(R^9)(R^{10}), carbocyclyl-C_1-C_8-alkyl, heterocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, or halogen-substituted heterocyclyl-C_1-C_8-alkyl.

[182] In some preferred embodiments, R^8 is -H, C_1-C_6-alkyl, -O-R^9, -N(R^9)(R^{10}), carbocyclyl-C_1-C_6-alkyl, heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, or halogen-substituted heterocyclyl-C_1-C_6-alkyl.

[183] In some preferred embodiments, R^8 is -H, C_1-C_6-alkyl, -O-R^9, -N(R^9)(R^{10}), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl.

[184] R^9 and R^{10} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halocarbocyclyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, haloheterocyclyl, and halogen-substituted heterocyclyl-C_1-C_8-alkyl.

[185] In some preferred embodiments, R^9 and R^{10} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halocarbocyclyl,

halogen-substituted carbocyclyl-C_1-C_6-alkyl, haloheterocyclyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl.

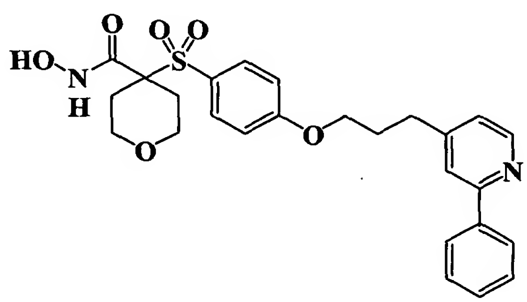
[186] In some preferred embodiments, R^9 and R^{10} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, and heterocyclyl, heterocyclyl-C_1-C_6-alkyl.

Preferred Embodiment No. 2-a: E^3 is optionally-substituted heterocyclyl

[187] In some embodiments, E^3 is optionally-substituted heterocyclyl.

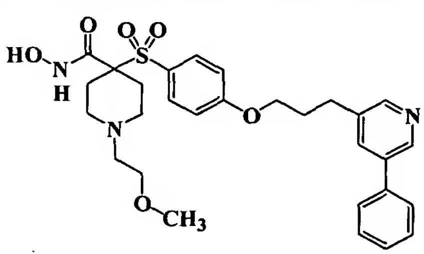
[188] In some preferred embodiments E^3 is an optionally-substituted heterocyclyl that contains only one heteroatom ring member. Examples of often suitable heterocyclyls include furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thiophenyl, dihydrothiophenyl, tetrahydrothiophenyl, pyrrolinyl, pyrrolyl, isopyrrolyl, pyrrolidinyl, pyridinyl, piperidinyl, pyranyl, dihydropyranyl, and tetrahydropyranyl.

[189] In some preferred embodiments, E^3 is optionally-substituted pyridinyl. In some such embodiments, E^5 is optionally-substituted phenyl. Such compounds include, for example:

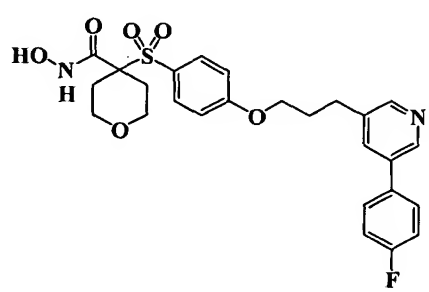


IIIA-1

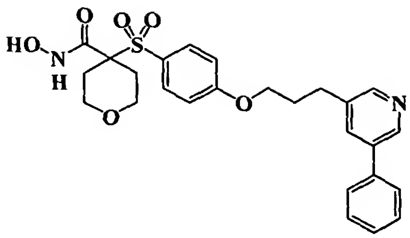
Such compounds also include, for example:



IIIA-2

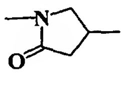


IIIA-3

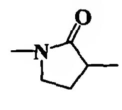


IIIA-4

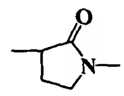
[190] In some preferred embodiments, E^3 is an optionally-substituted heterocyclyl selected from the group consisting of:



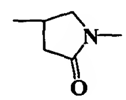
E-1



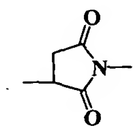
E-2



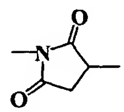
E-3



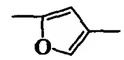
E-4



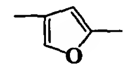
E-5



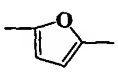
E-6



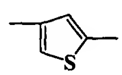
E-7



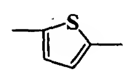
E-8



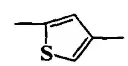
E-9



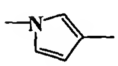
E-10



E-11



E-12



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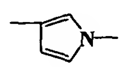
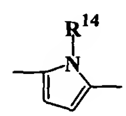
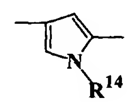


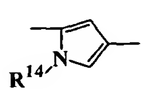
E-14



E-15



E-16

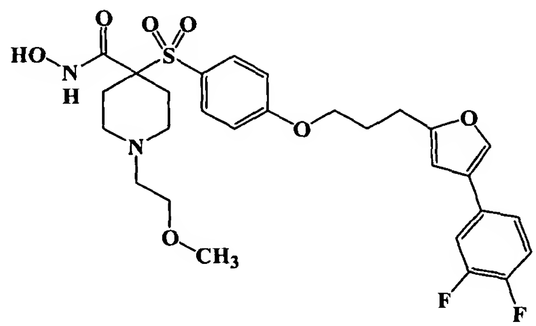


E-17

Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the substituent is halogen or -OH, any substituent of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylthio, halo-C_1-C_6-alkyl,

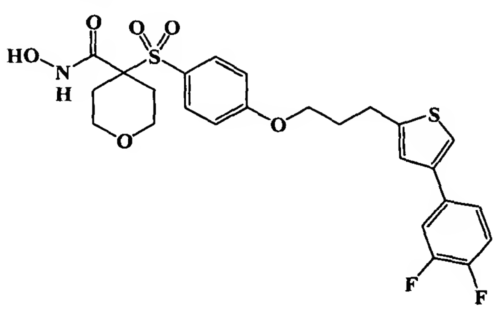
halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and halo-C_1-C_6-alkylthio. R^{14} is selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is halogen or -OH, any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylthio, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and halo-C_1-C_6-alkylthio.

[191] In some preferred embodiments, E^3 is optionally-substituted furanyl. In one such embodiment, for example, E^5 is optionally-substituted phenyl. Such compounds include, for example:

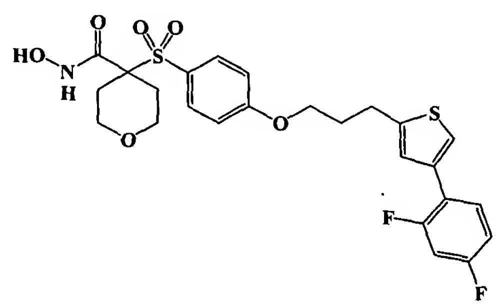


IIIA-5

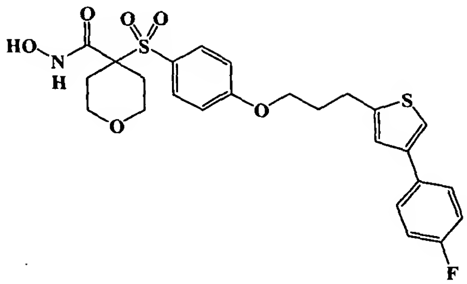
[192] In some preferred embodiments, E^3 is optionally-substituted thienyl. In some such embodiments, E^5 is optionally-substituted phenyl. Such compounds include, for example:



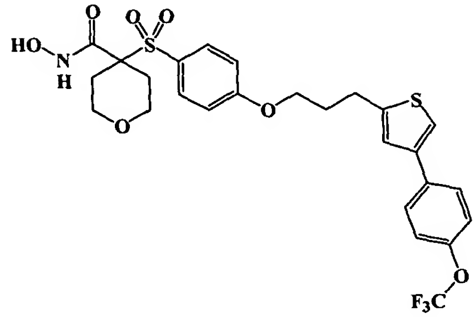
IIIA-6



IIIA-7

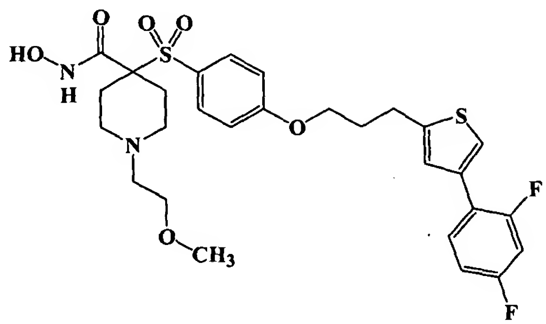


IIIA-8



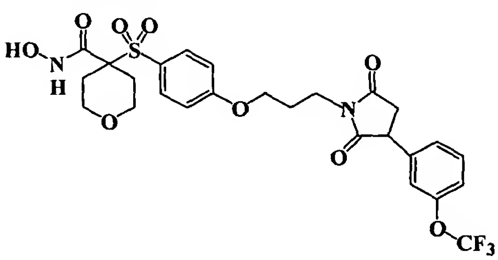
IIIA-9

Such compounds also include, for example:

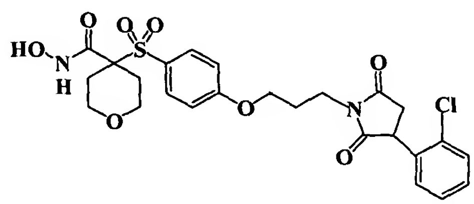


IIIA-10

[193] In some preferred embodiments, E^3 is optionally-substituted pyrrolidinyl. In some such embodiments, for example, E^5 is optionally-substituted phenyl. Such compounds include, for example:



IIIA-11

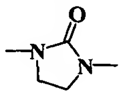


IIIA-12

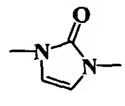
[194] E^3 also may be, for example, an optionally-substituted heterocyclyl that contains no greater and no less than two heteroatom ring members. Suitable heterocyclyls include, for example, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, dithiolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, oxathiolyl, oxathiolanyl, oxazolyl, isoxazolyl, oxazolidinyl,

isoxazolidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazinyl, and morpholinyl.

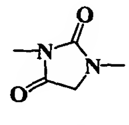
[195] In some preferred embodiments, E^3 is an optionally-substituted heterocyclyl selected from the group consisting of:



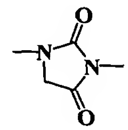
E-18



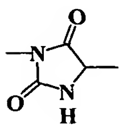
E-19



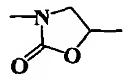
E-20



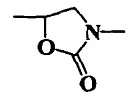
E-21



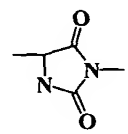
E-22



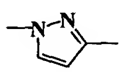
E-23



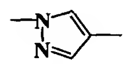
E-24



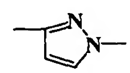
E-25



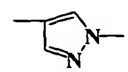
E-1



E-1



E-1



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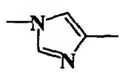

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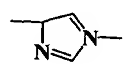

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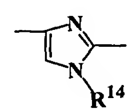

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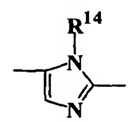
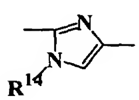
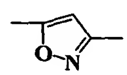


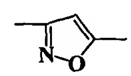
E-29



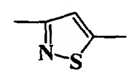
E-30



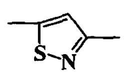
E-31



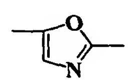
E-32



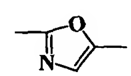
E-33



E-34



E-35



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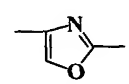

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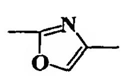

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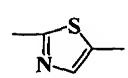

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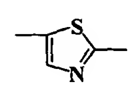

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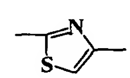
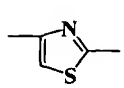


E-41

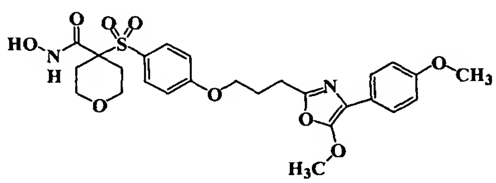


E-42

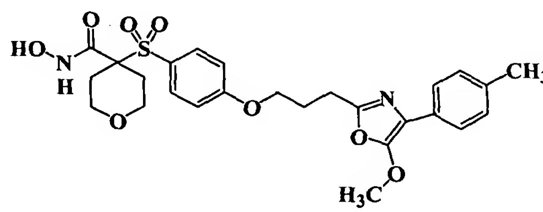
Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl,

C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the substituent is halogen or -OH, any substituent of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylthio, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and halo-C_1-C_6-alkylthio. Such substituents also optionally are substituted with one or more substituents independently selected from the group consisting of C_2-C_6-alkenyl and C_2-C_6-alkynyl. R^{14} is as defined above where E^3 contains only one heteroatom in its ring.

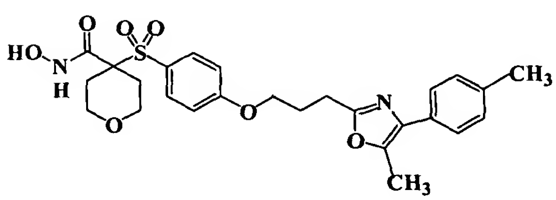
[196] In some particularly preferred embodiments, E^3 is an optionally-substituted heterocyclyl selected from the group consisting of oxazolyl and isoxazolyl. In some such embodiment, for example, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



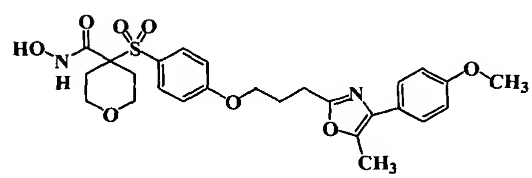
IIIA-13



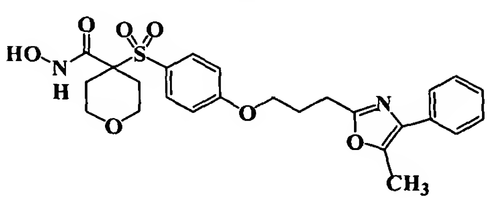
IIIA-14



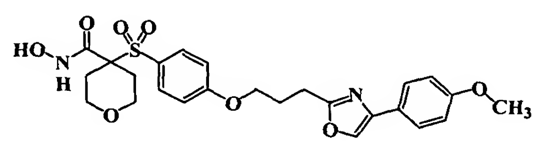
IIIA-15



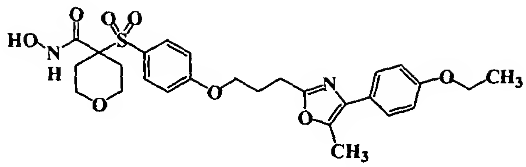
IIIA-16



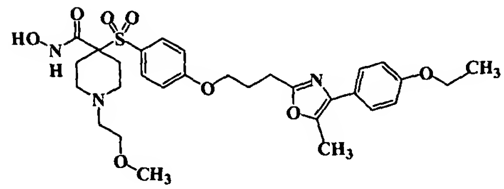
IIIA-17



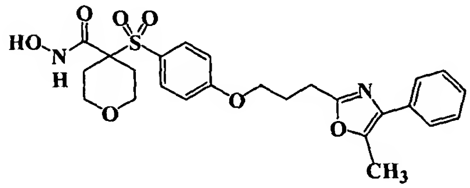
IIIA-18



IIIA-19

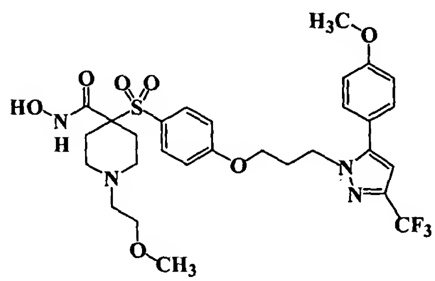


IIIA-20

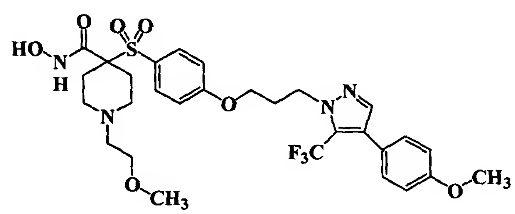


IIIA-21

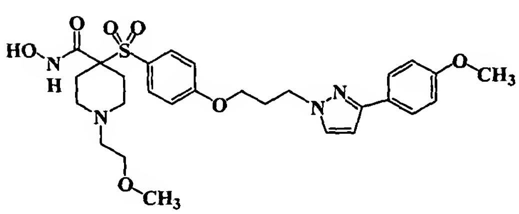
[197] In some preferred embodiments, E^3 is an optionally-substituted heteroaryl selected from the group consisting of pyrazolyl and isoimidazolyl. In some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



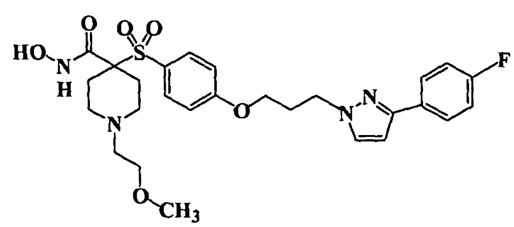
IIIA-22



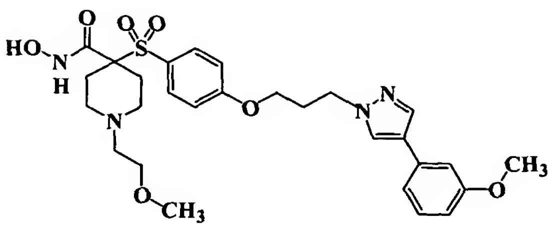
IIIA-23



IIIA-24

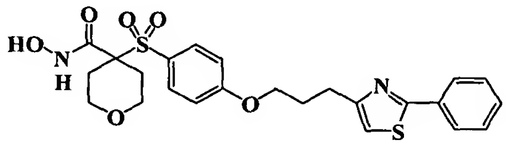


IIIA-25



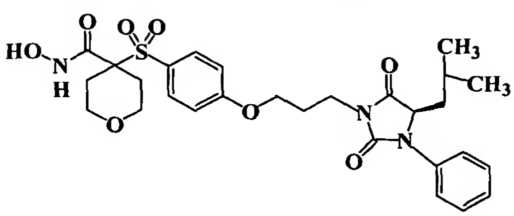
IIIA-26

[198] In some preferred embodiments, E^3 is an optionally-substituted heteroaryl selected from the group consisting of thiazolyl and isothiazolyl. In one such embodiment, for example, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:

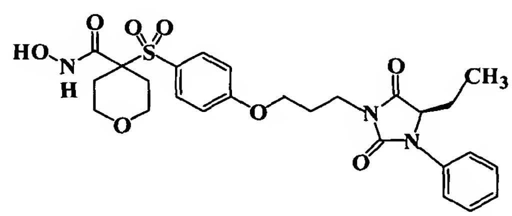


IIIA-27

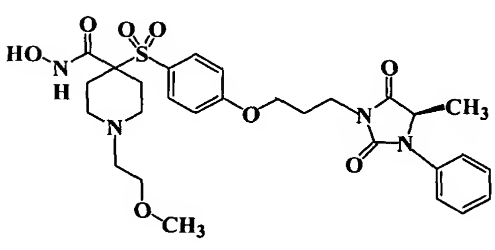
[199] In some preferred embodiments, E^3 is an optionally-substituted heteroaryl selected from the group consisting of pyrazolidinyl and imidazolidinyl. In some such embodiments, E^5 is optionally-substituted carbocyclyl. In some preferred embodiments, E^5 is optionally-substituted aryl, often preferably optionally-substituted phenyl. Such compounds include, for example:



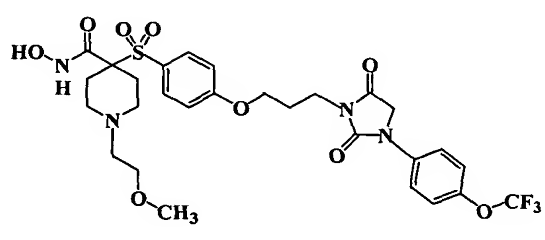
IIIA-28



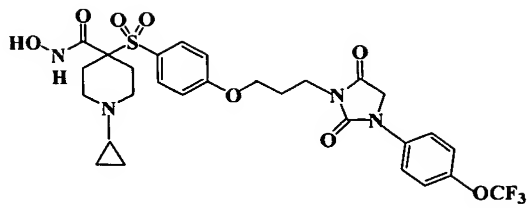
IIIA-29



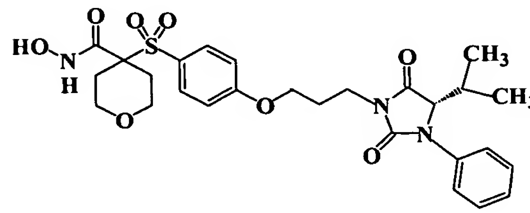
IIIA-30



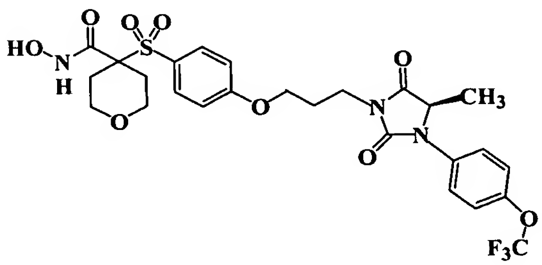
IIIA-31



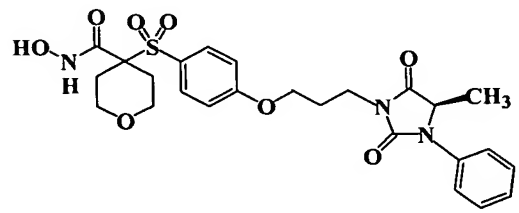
IIIA-32



IIIA-33



IIIA-34



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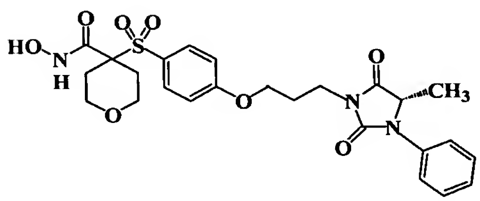
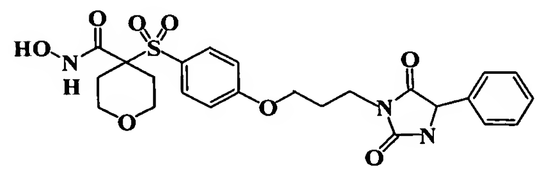
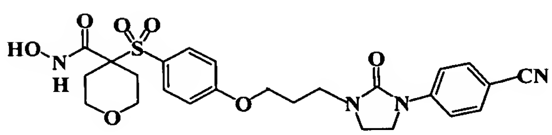


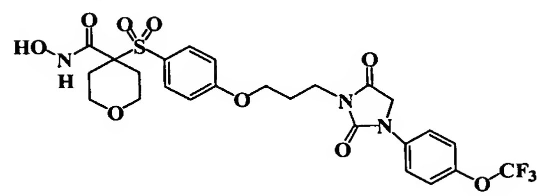
IIIA-36



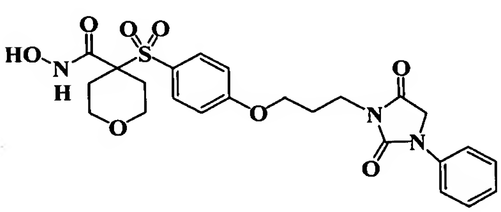
IIIA-37



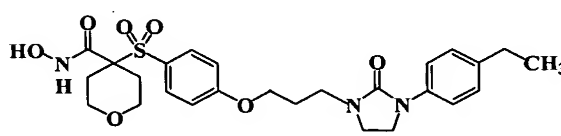
IIIA-38



IIIA-39



IIIA-40



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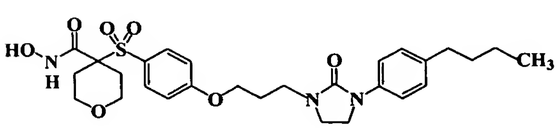

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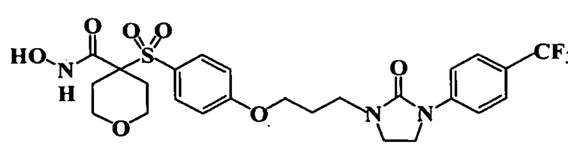
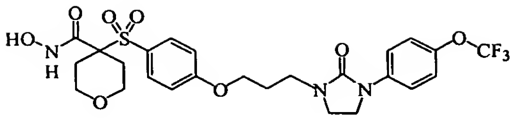


IIIA-43



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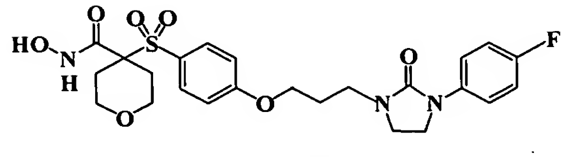
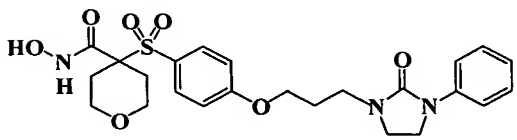
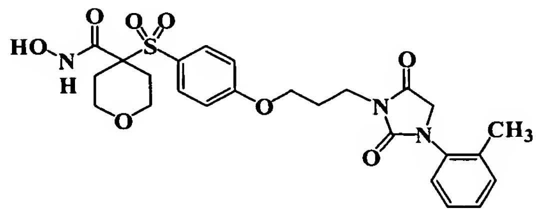


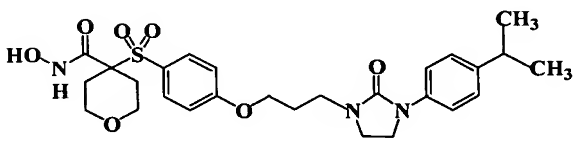
IIIA-45



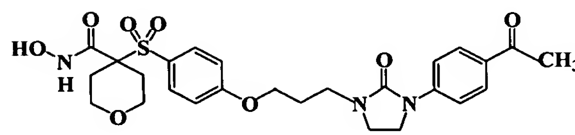
IIIA-46



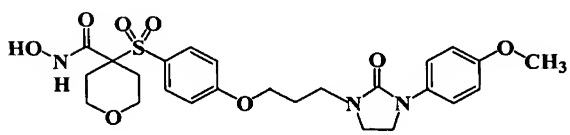
IIIA-47



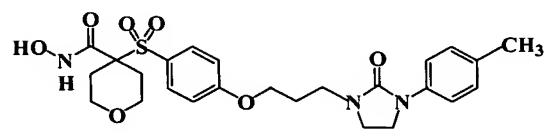
IIIA-48



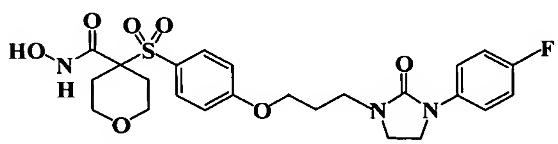
IIIA-49



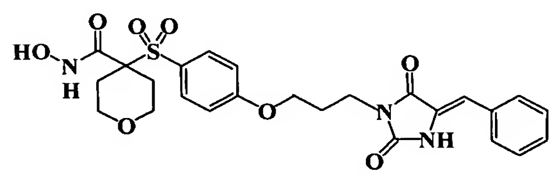
IIIA-50



IIIA-51

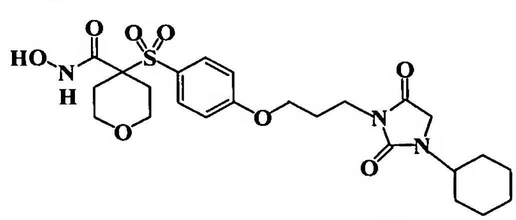


IIIA-52



IIIA-53

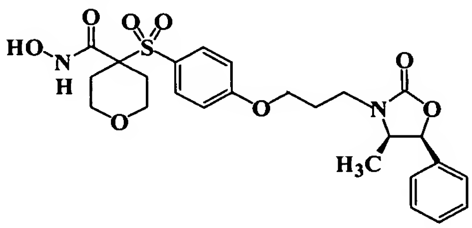
In other preferred embodiments, E^5 is optionally substituted C_5-C_6-cycloalkyl. Such compounds include, for example:



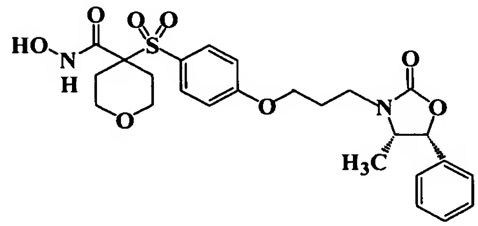
IIIA-54

[200] In some preferred embodiments, E^3 is optionally-substituted oxazolidinyl. In some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably

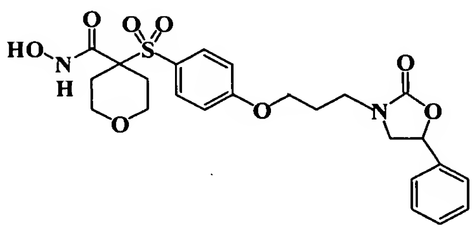
optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



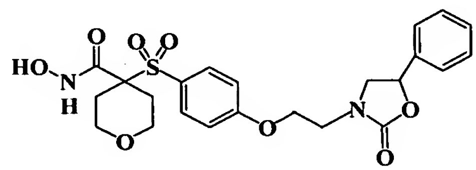
IIIA-55



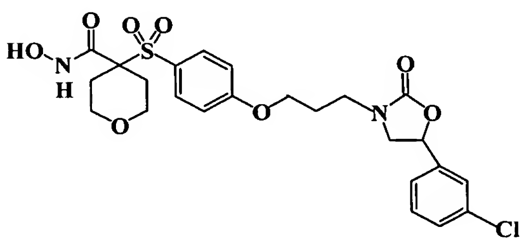
IIIA-56



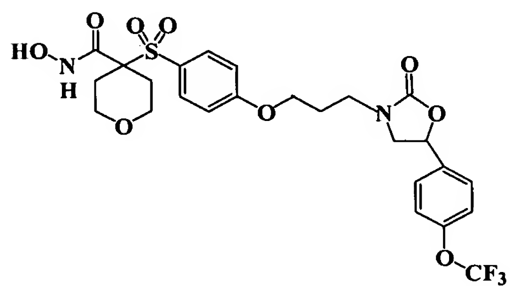
IIIA-57



IIIA-58



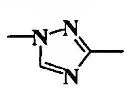
IIIA-59



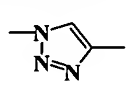
IIIA-60

[201] E^3 also may be, for example, an optionally-substituted heterocyclyl that contains no greater and no less than 3 heteroatom ring members. Often suitable heterocyclyls include, for example, oxadiazolyl, thiadiazolyl, and triazolyl. Here, the triazolyl optionally is substituted.

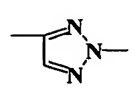
[202] In some preferred embodiments, E^3 is an optionally-substituted heteroaryl selected from the group consisting of:



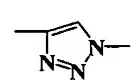
E-43



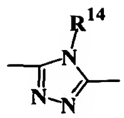
E-44

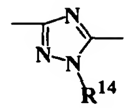


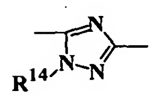
E-45

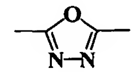


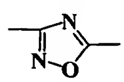
E-46

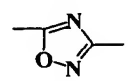

E-47

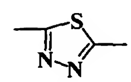

E-48

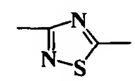

E-49

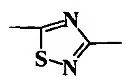

E-50


E-51


E-52


E-53

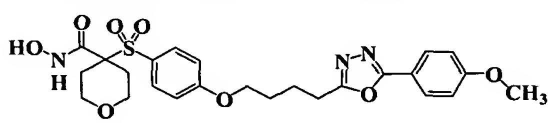

E-54

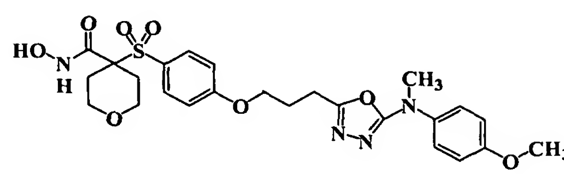

E-55

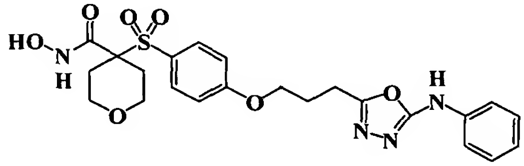
Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the substituent is halogen or -OH, any substituent of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylthio, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and halo-C_1-C_6-alkylthio. R^{14} is as defined above for heterocyclyls containing 1 or 2 heteroatom ring members.

[203] In some preferred embodiments, E^3 is oxadiazolyl.

[204] In some such embodiments, E^5 is optionally-substituted phenyl. Such compounds include, for example:


IIIA-61


IIIA-62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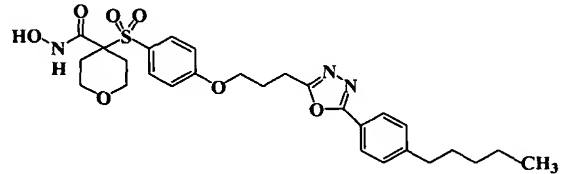
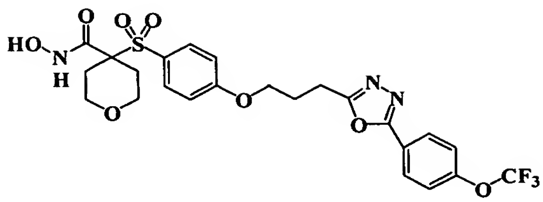
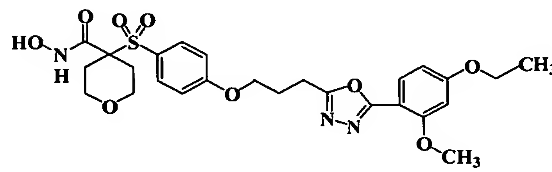
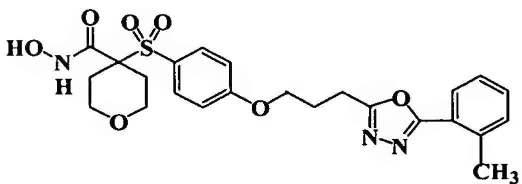

IIIA-64



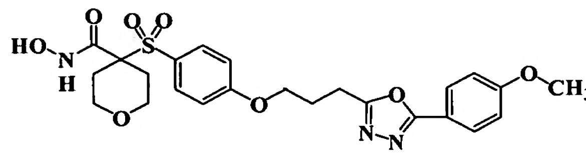
IIIA-65



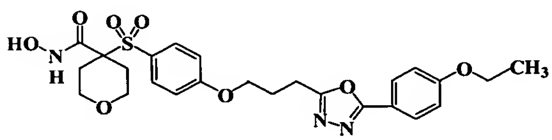
IIIA-66



IIIA-67



IIIA-68



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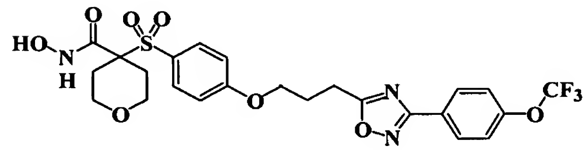

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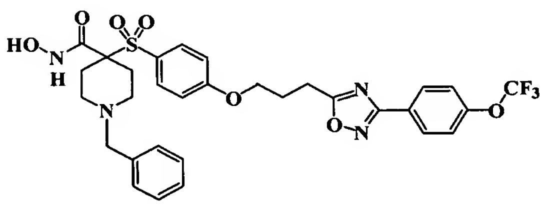
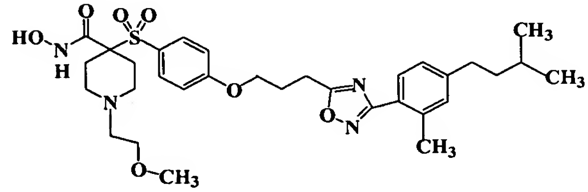


IIIA-71



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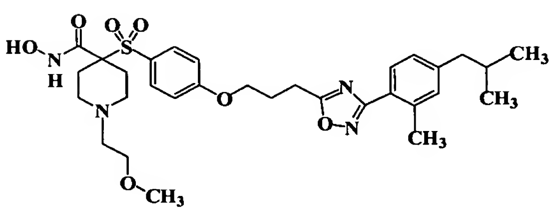

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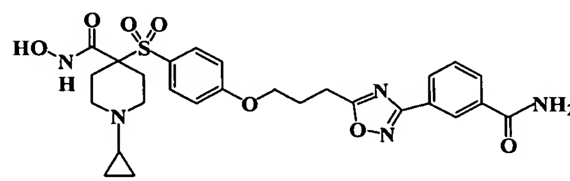

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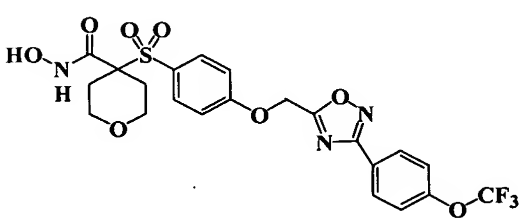

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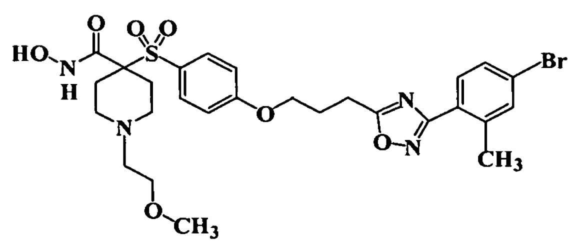

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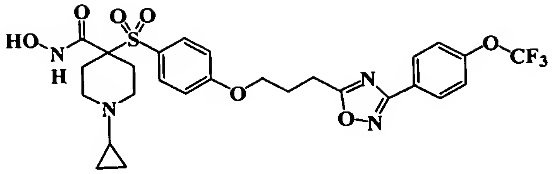

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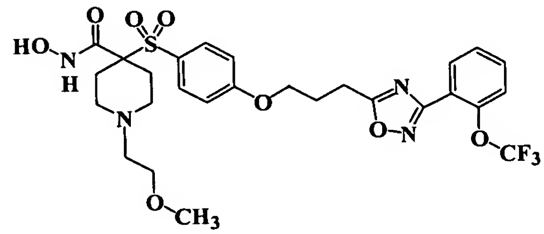

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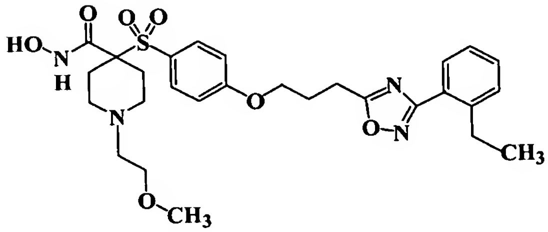

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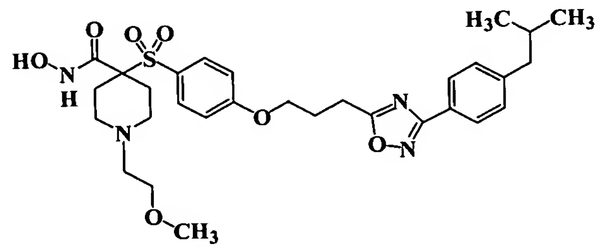

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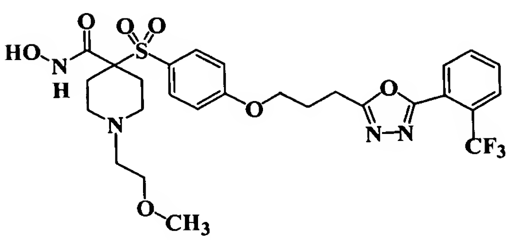

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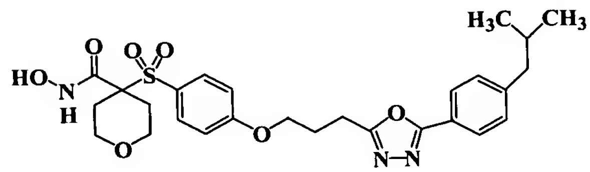

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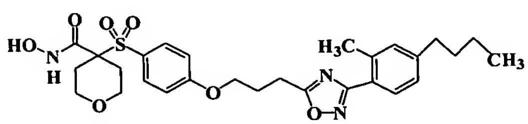

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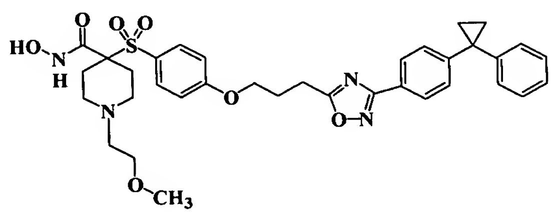

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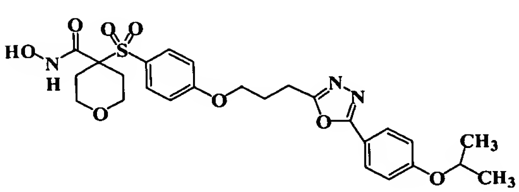

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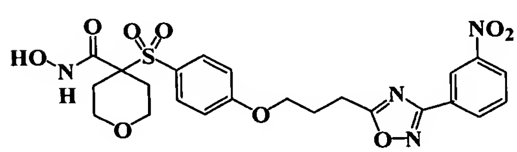

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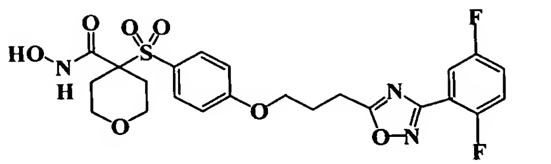

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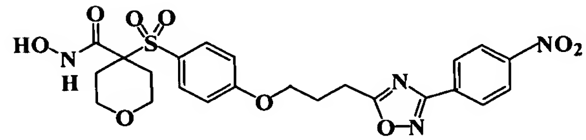

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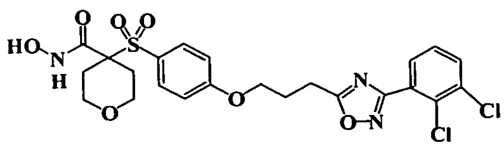

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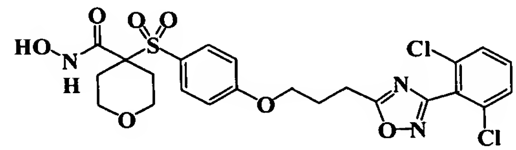

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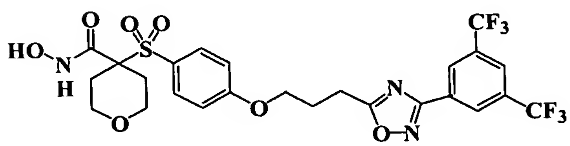

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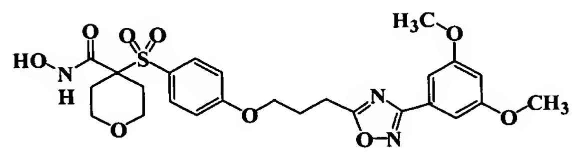

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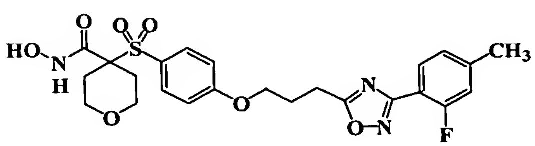

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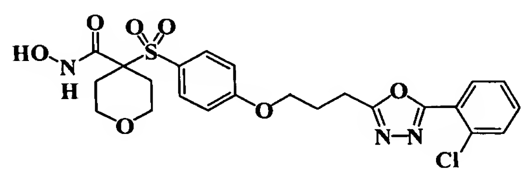

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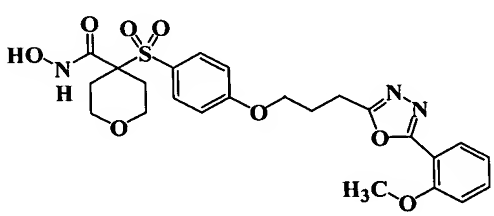
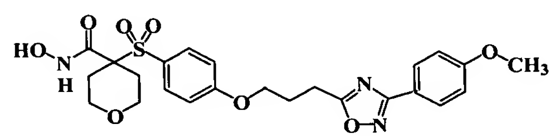
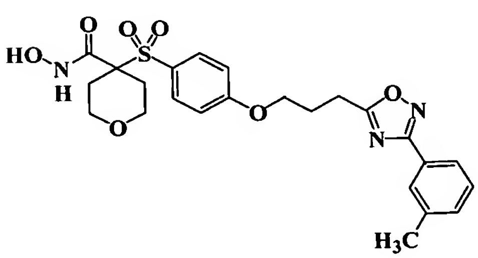


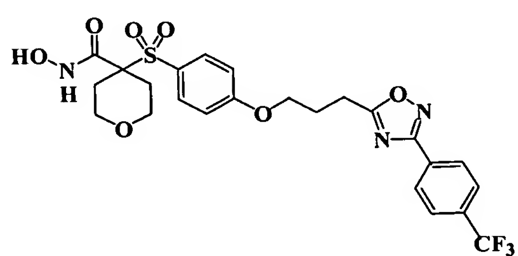
IIIA-95



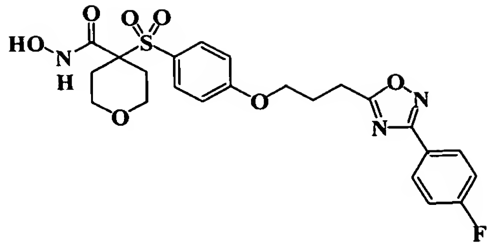
IIIA-96



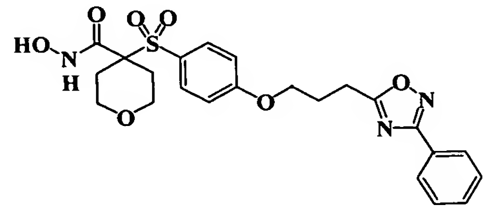
IIIA-97



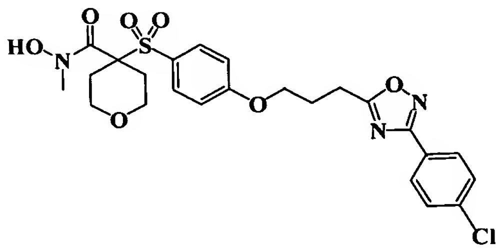
IIIA-98



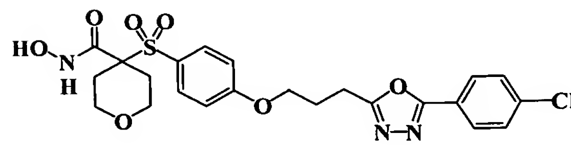
IIIA-99



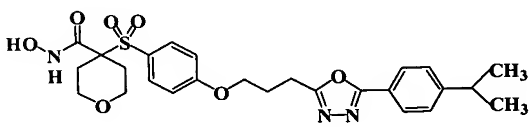
IIIA-100



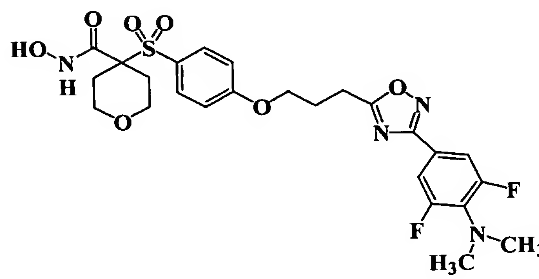
IIIA-101



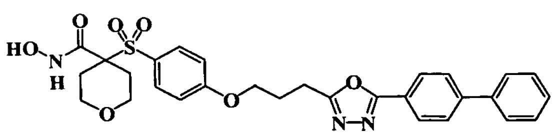
IIIA-102



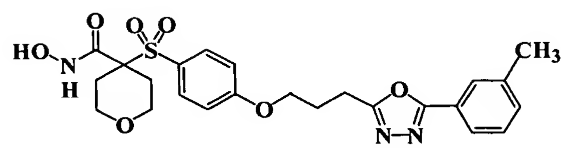
IIIA-103



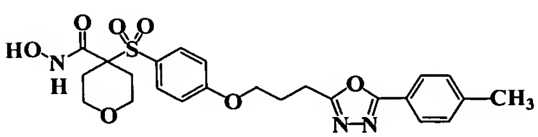
IIIA-104



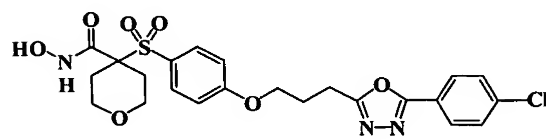
IIIA-105



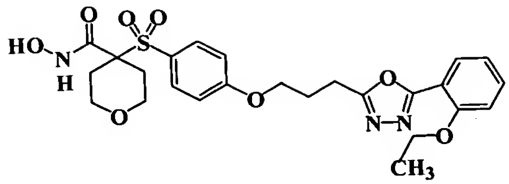
IIIA-106



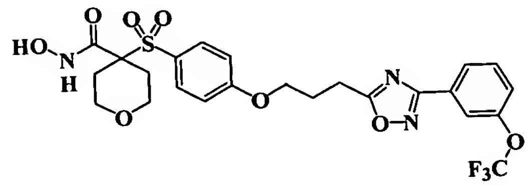
IIIA-107



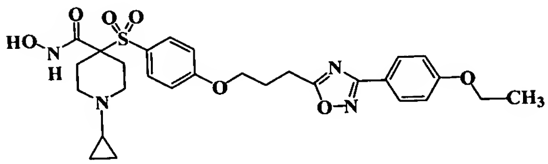
IIIA-108



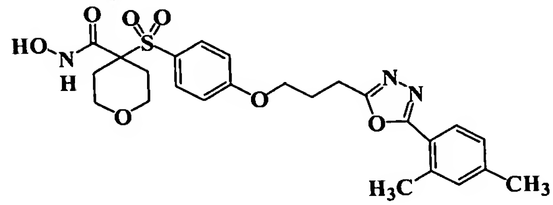
IIIA-109



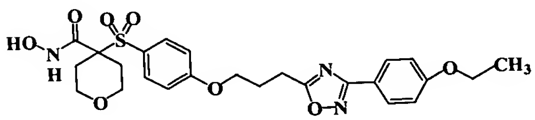
IIIA-110



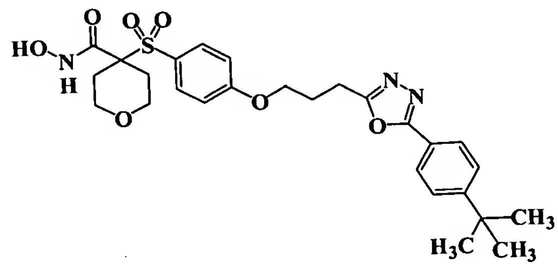
IIIA-111



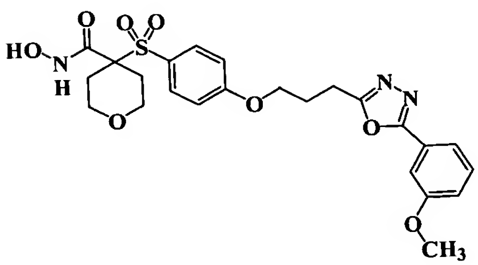
IIIA-112



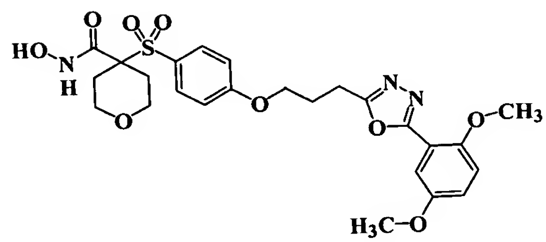
IIIA-113



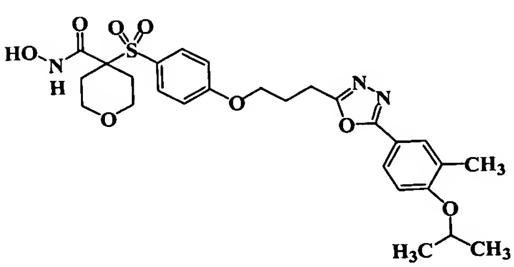
IIIA-114



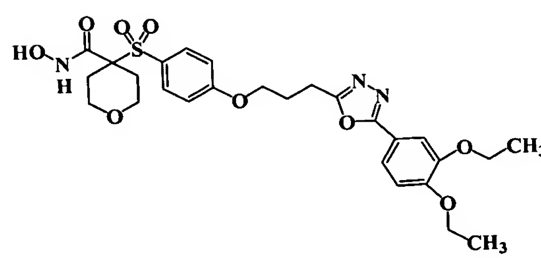
IIIA-115



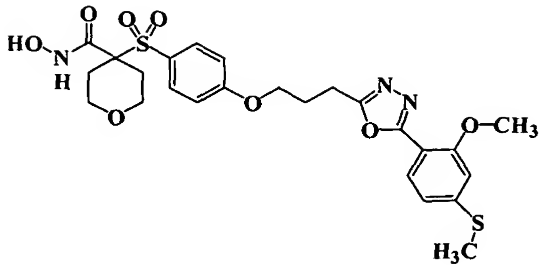
IIIA-116



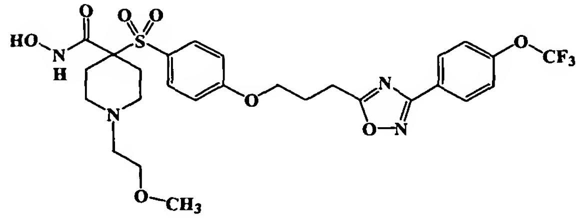
IIIA-117



IIIA-118

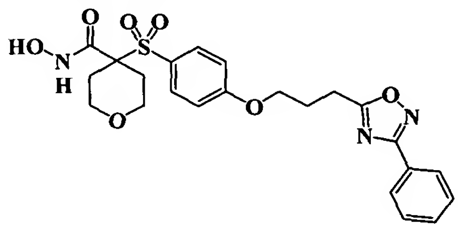


IIIA-119

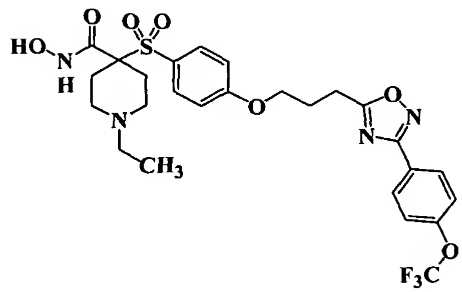


IIIA-120

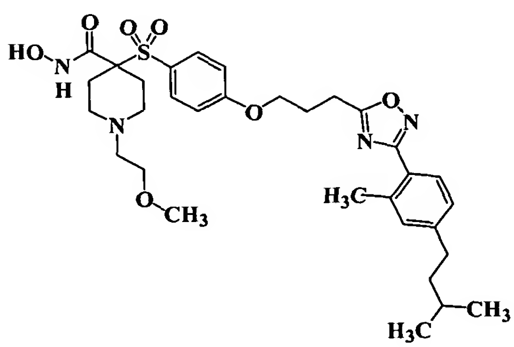
Such compounds also include, for example:



IIIA-121

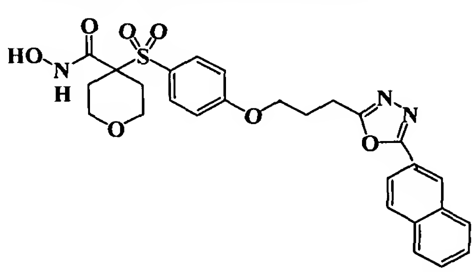


IIIA-122

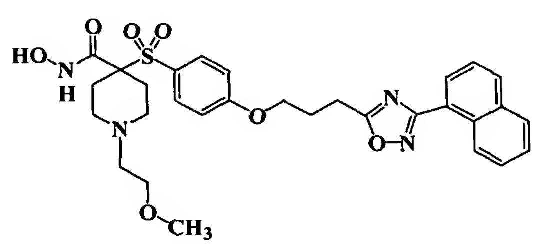


IIIA-123

[205] In other embodiments, E^5 is optionally-substituted naphthalenyl. Such compounds include, for example:

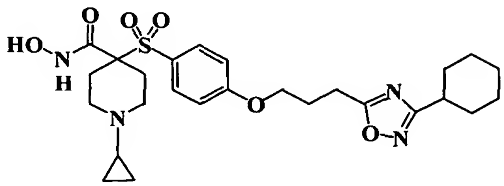


IIIA-124

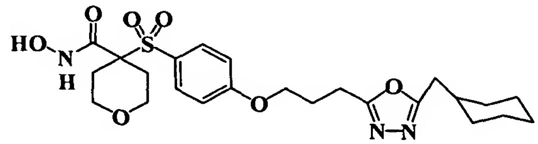


IIIA-125

[206] In other embodiments, E^5 is optionally-substituted C_5-C_6-cycloalkyl. Such compounds include, for example:

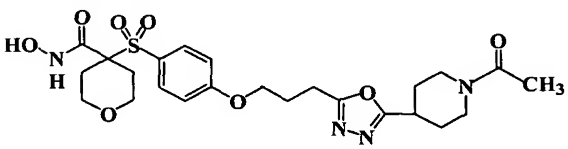


IIIA-126

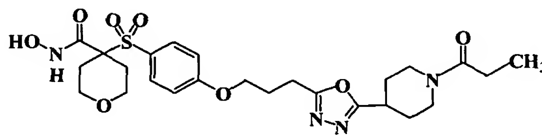


IIIA-127

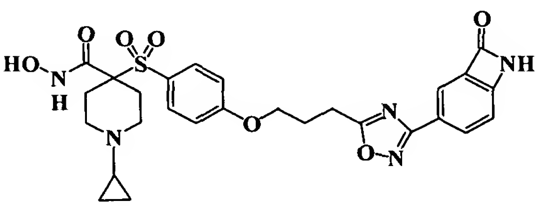
[207] In yet other embodiments, E^5 is optionally-substituted heterocyclyl. Such compounds include, for example:



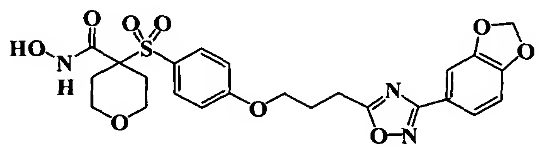
IIIA-128



IIIA-129

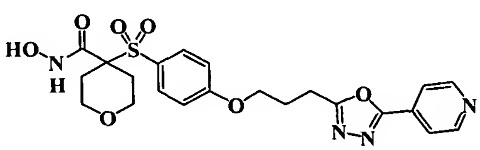


IIIA-130

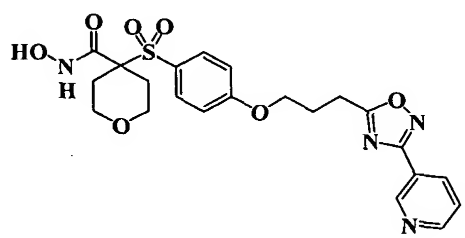


IIIA-131

Such compounds also include, for example:



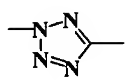
IIIA-132



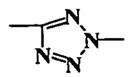
IIIA-133

[208] E^3 also may be, for example, an optionally-substituted heterocyclyl that contains at least 4 heteroatom ring members.

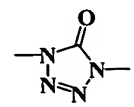
[209] In some preferred embodiments, E^3 is selected from the group consisting of:



E-56

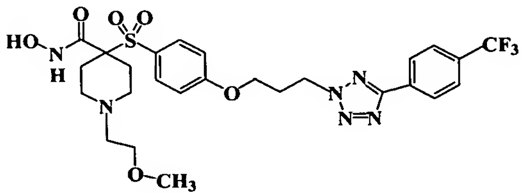


E-57

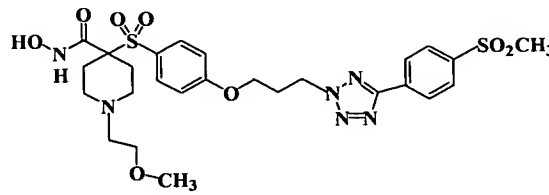


E-58

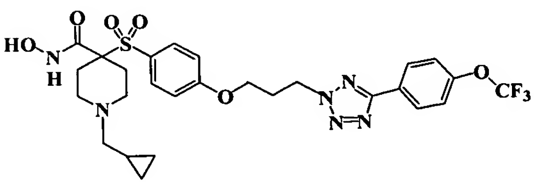
In some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



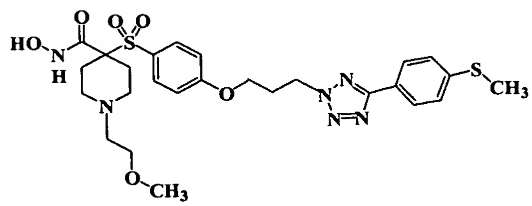
IIIA-134



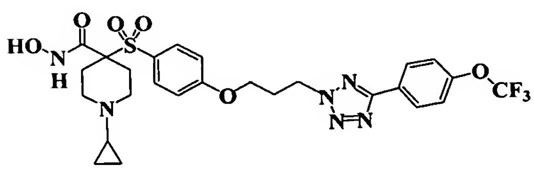
IIIA-135



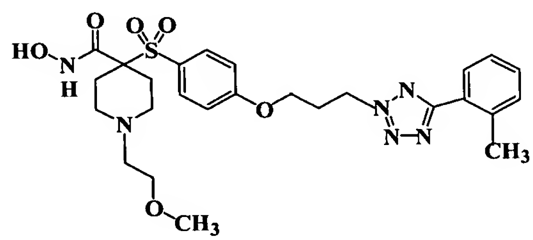
IIIA-136



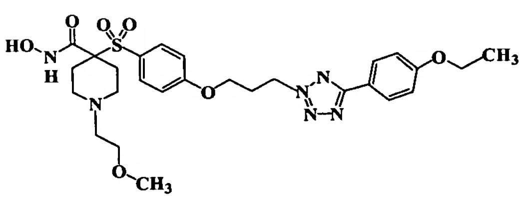
IIIA-137



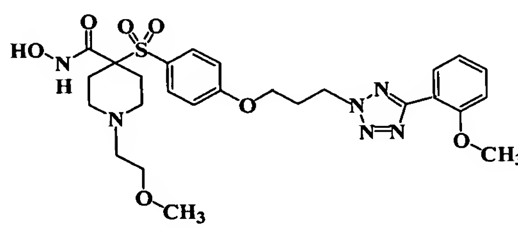
IIIA-138



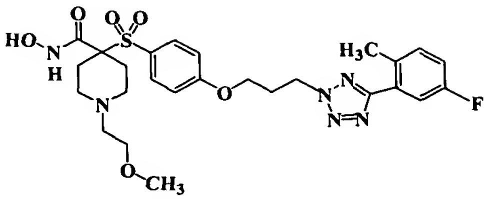
IIIA-139



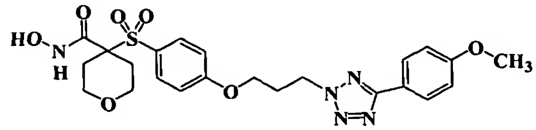
IIIA-140



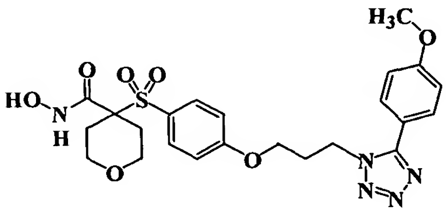
IIIA-141



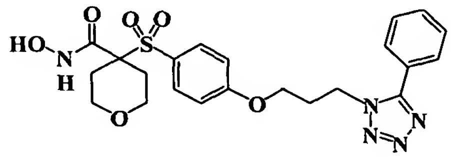
IIIA-142



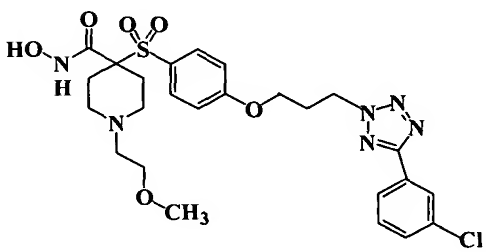
IIIA-143



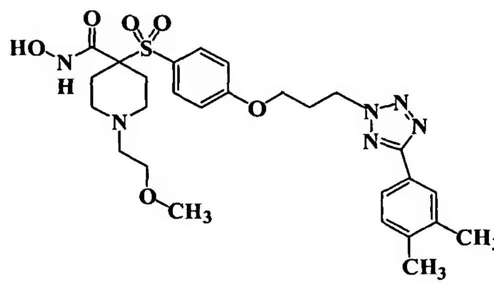
IIIA-144



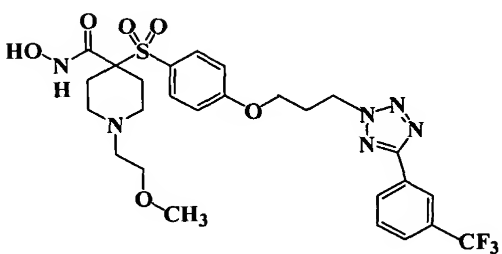
IIIA-145



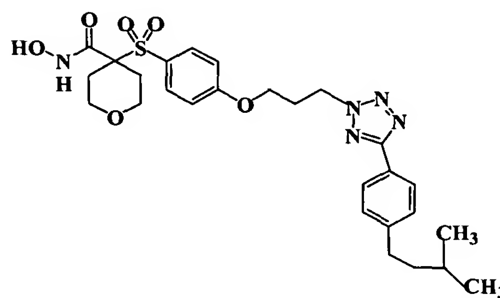
IIIA-146



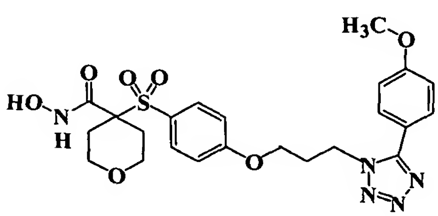
IIIA-147



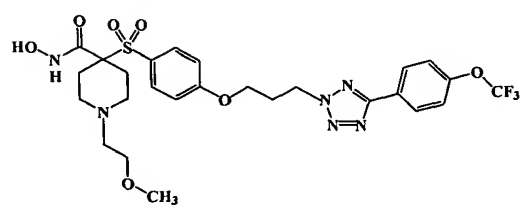
IIIA-148



IIIA-149

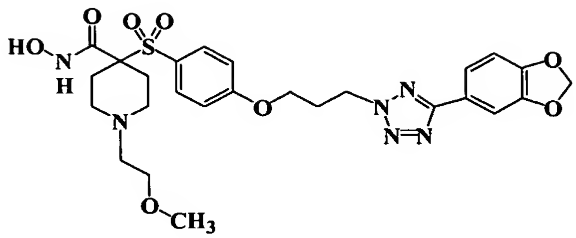


IIIA-150

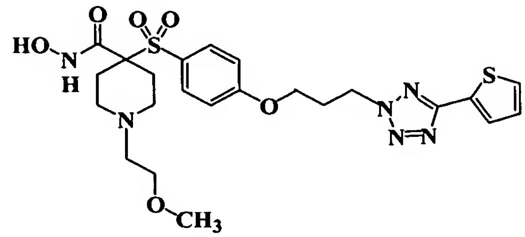


IIIA-151

In other such embodiments, E^5 is optionally-substituted heterocyclyl. Such compounds include, for example:



IIIA-152



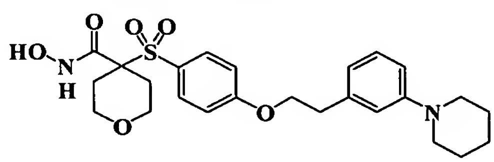
IIIA-153

Preferred Embodiment No. 2-b: E^3 is optionally substituted carbocyclyl

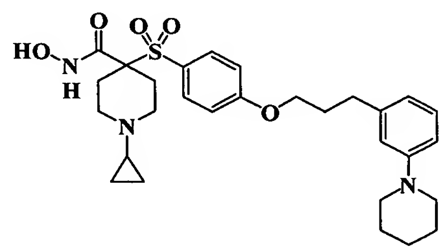
[210] In some embodiments, E^3 is an optionally-substituted carbocyclyl. E^3 may be, for example, an optionally-substituted carbocyclyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, phenyl, naphthalenyl, tetrahydronaphthalenyl, indenyl, isoindenyl, indanyl, bicyclodecanyl, anthracenyl, phenanthrene, benzonaphthenyl, fluoreneyl, decalinyl, and norpinanyl.

[211] In some preferred embodiments, E^3 is optionally-substituted phenyl. In one such embodiment, for example, E^5 is optionally-substituted heterocyclyl.

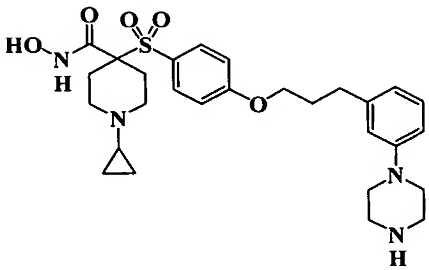
[212] In some such embodiments, E^5 is optionally-substituted heterocycloalkyl. Examples of such compounds include, for example:



IIIB-1

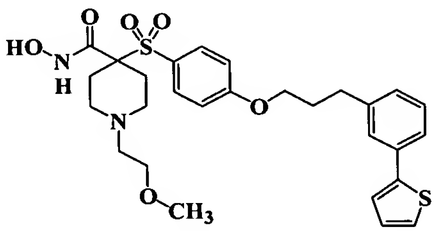


IIIB-2

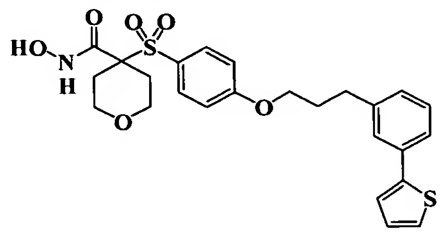


IIIB-3

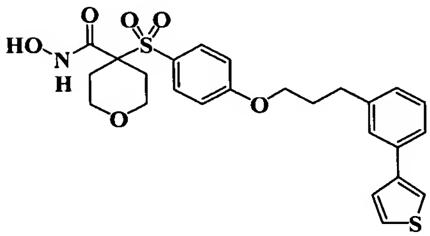
[213] In other preferred embodiments, E^5 is optionally-substituted, 5-member heteroaryl. Examples of such compounds include, for example:



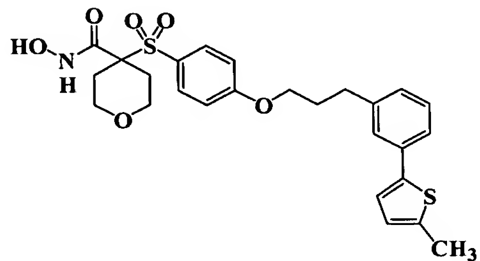
IIIB-4



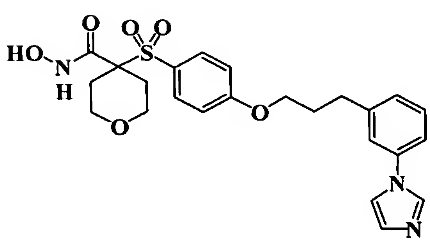
IIIB-5



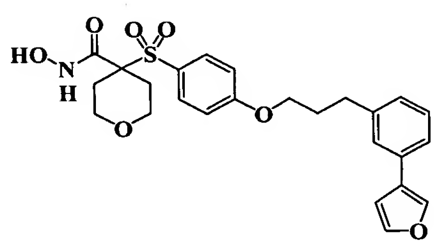
IIIB-6



IIIB-7

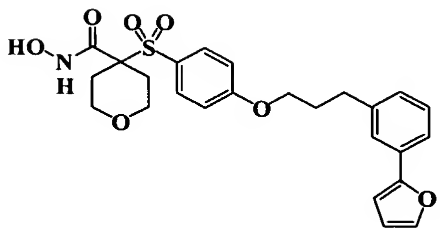


IIIB-8



IIIB-9

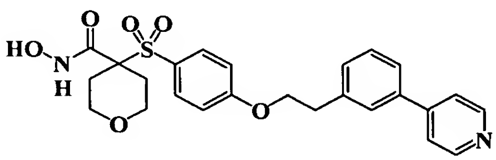
Such compounds also include, for example:



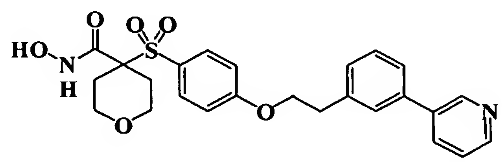
IIIB-10

[214] In other preferred embodiments, E^5 is optionally-substituted, 6-member heteroaryl.

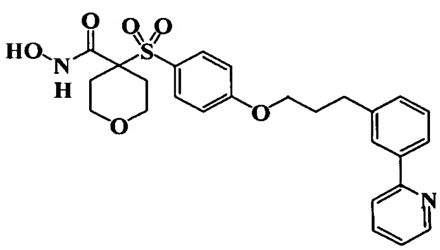
[215] In other preferred embodiments, E^5 is optionally-substituted pyridinyl. Such compounds include, for example:



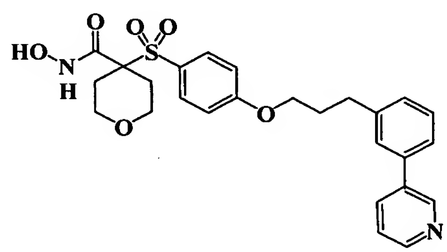
IIIB-11



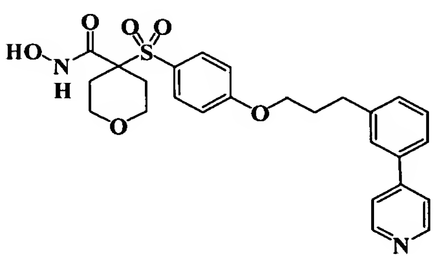
IIIB-12



IIIB-13

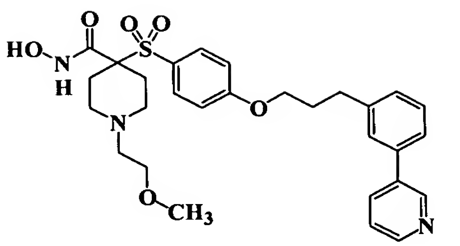


IIIB-14

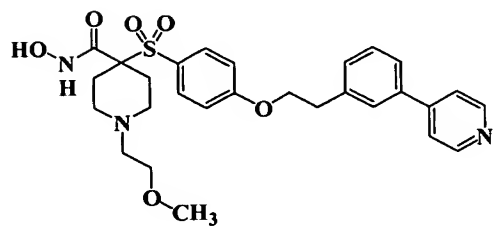


IIIB-15

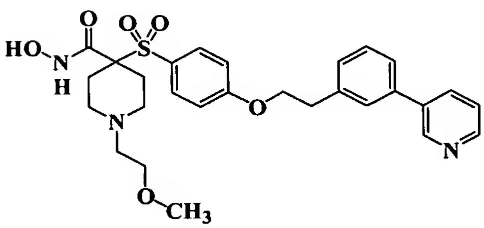
Such compounds also include, for example:



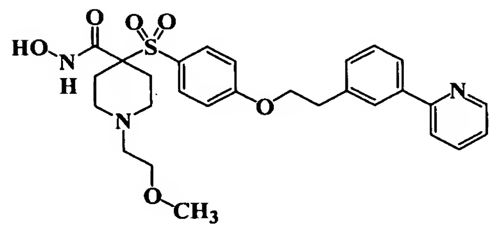
IIIB-16



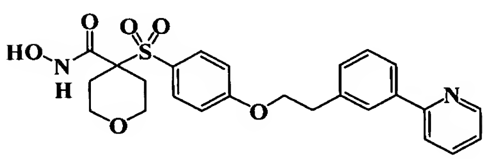
IIIB-17



IIIB-18

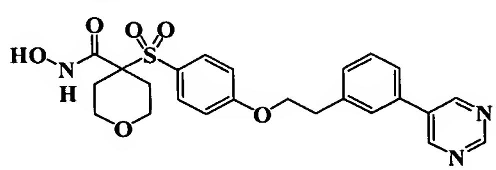


IIIB-19



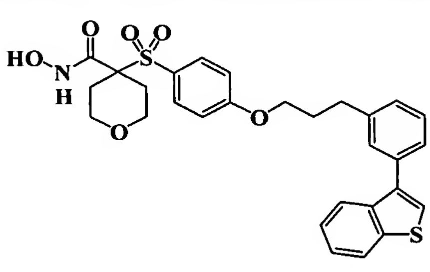
IIIB-20

[216] In other preferred embodiments, E^5 is optionally-substituted pyrimidinyl. Such compounds include, for example:

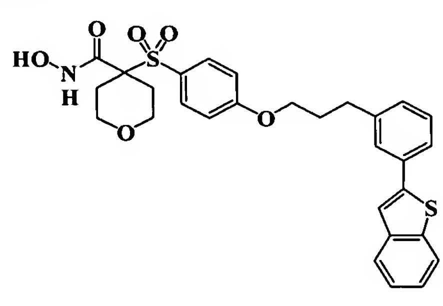


IIIB-21

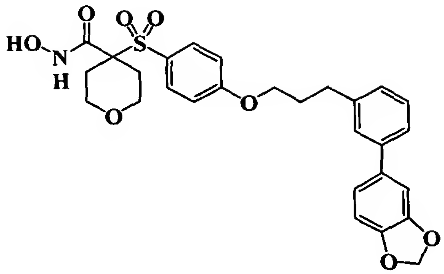
[217] In other preferred embodiments, E^5 is optionally-substituted, multi-ring heterocyclyl. Such compounds include, for example:



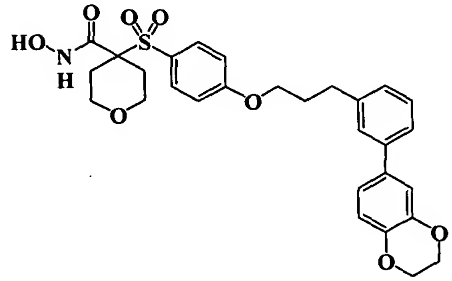
IIIB-22



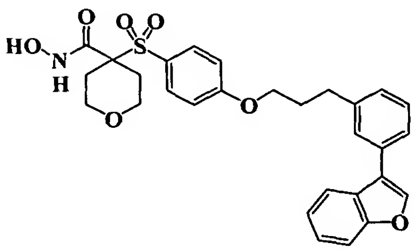
IIIB-23



IIIB-24



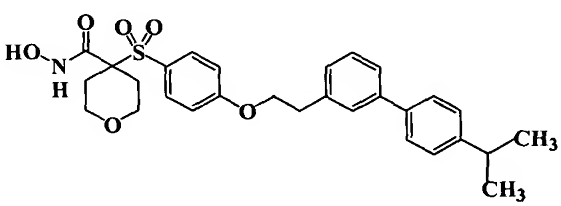
IIIB-25



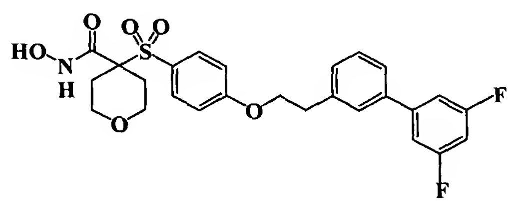
IIIB-26

[218] In some preferred embodiments, for example, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl,

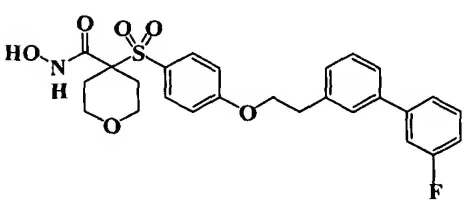
[219] In some preferred embodiments, E^5 is optionally-substituted phenyl. Such compounds include, for example:



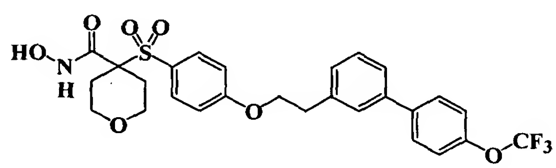
IIIB-27



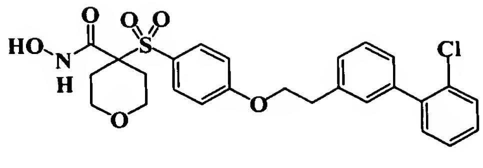
IIIB-28



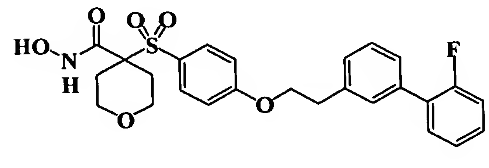
IIIB-29



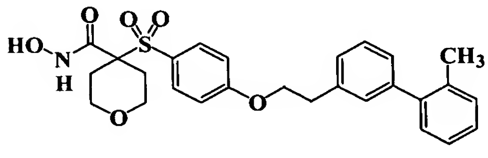
IIIB-30



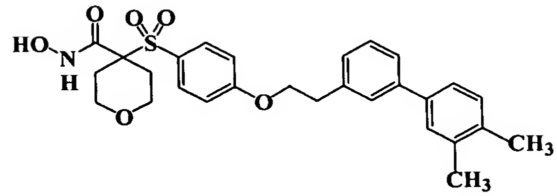
IIIB-31



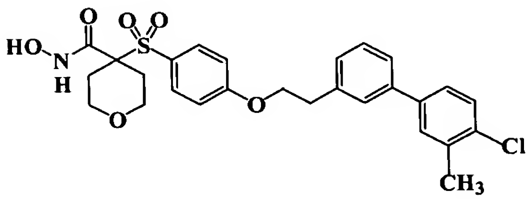
IIIB-32



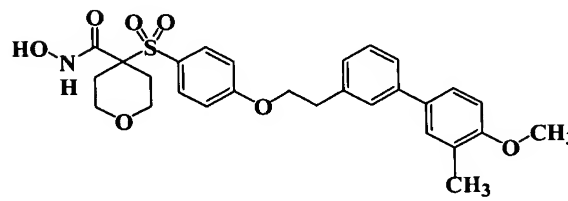
IIIB-33



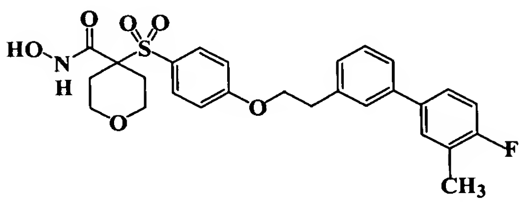
IIIB-34



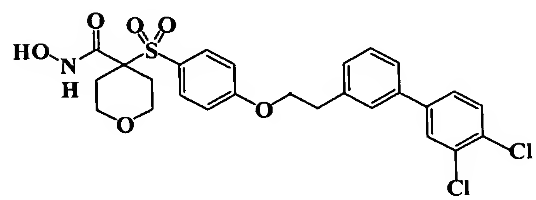
IIIB-35



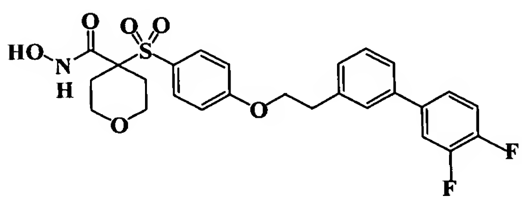
IIIB-36



IIIB-37



IIIB-38



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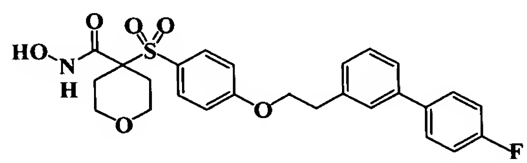
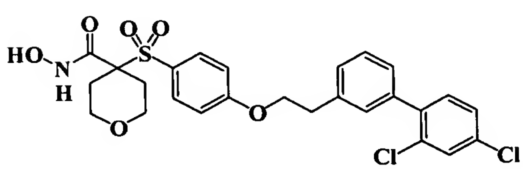


IIIB-40



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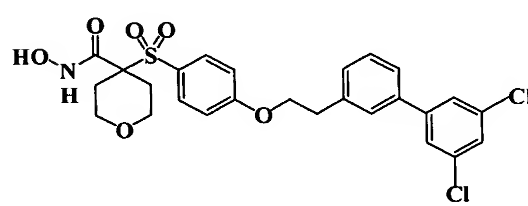

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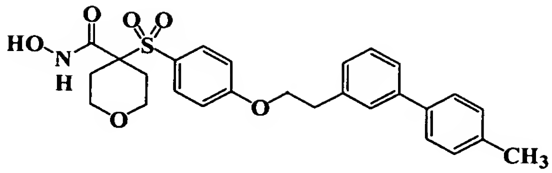

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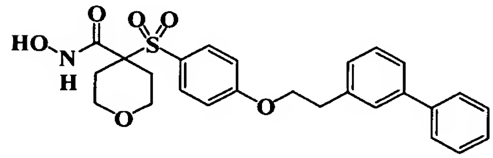
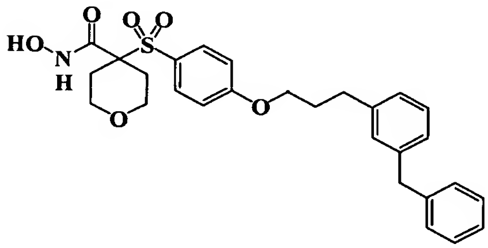


IIIB-44



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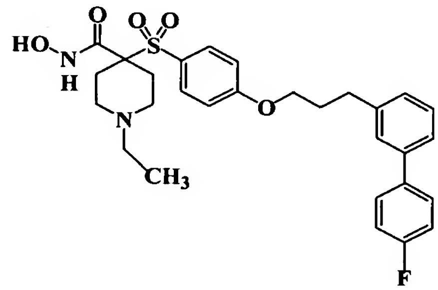

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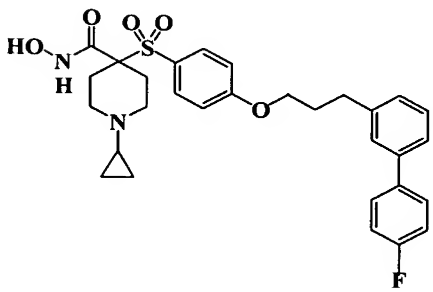
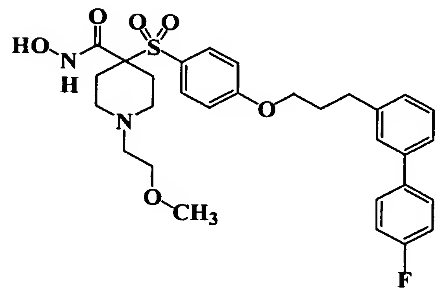


IIIB-47



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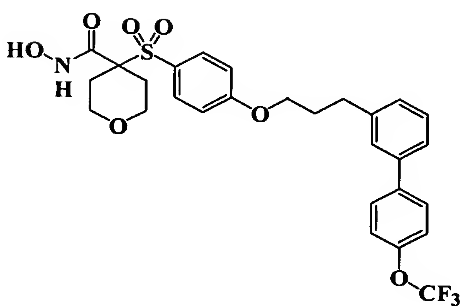

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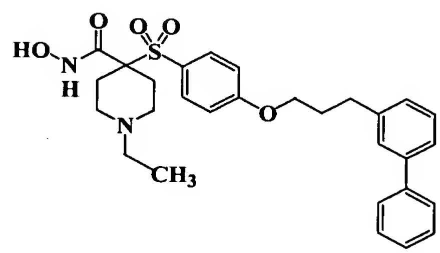

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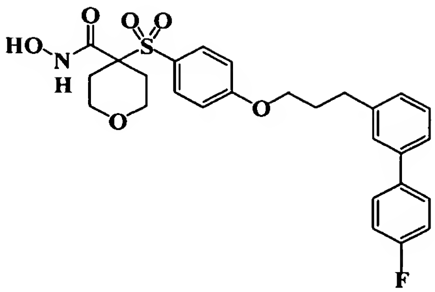

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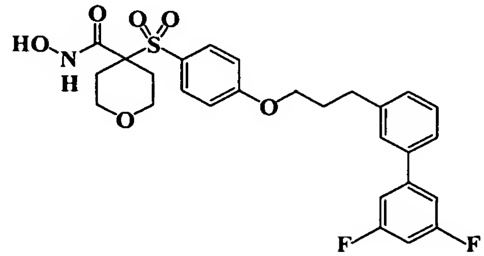

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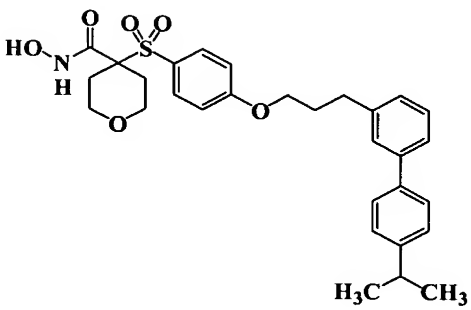

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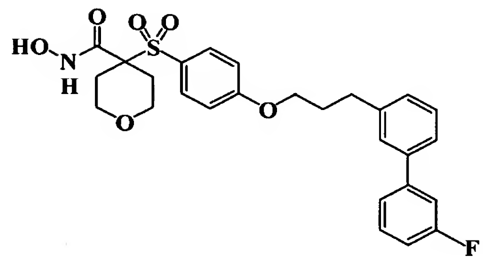

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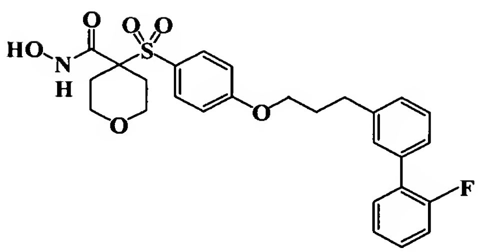

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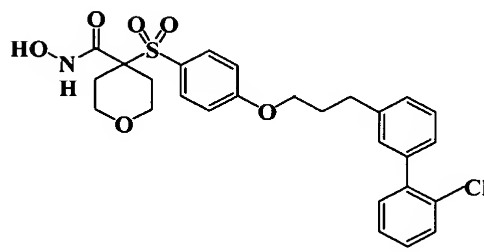

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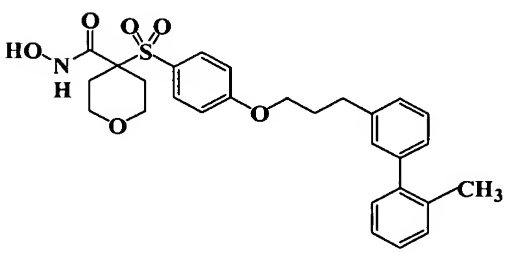

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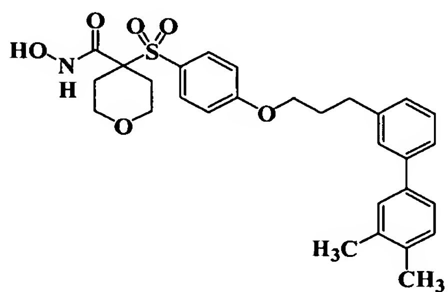
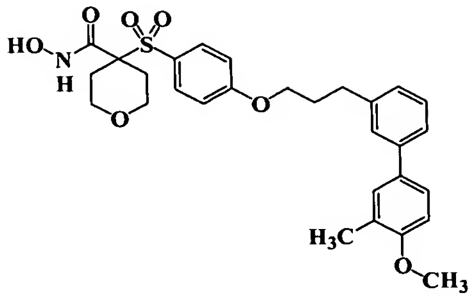
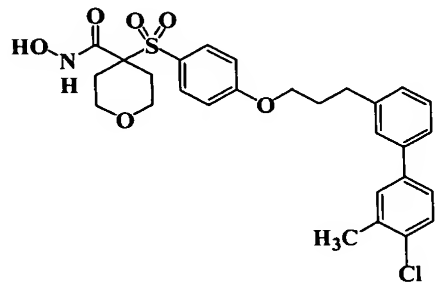


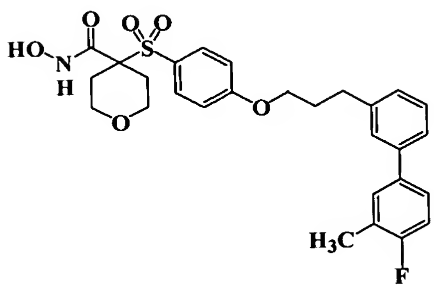
IIIB-58



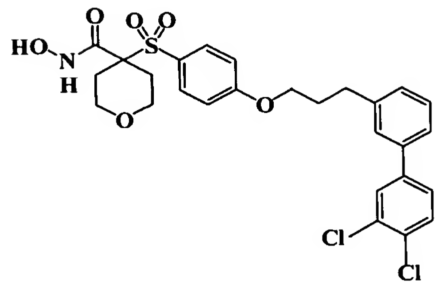
IIIB-59



IIIB-60



IIIB-61



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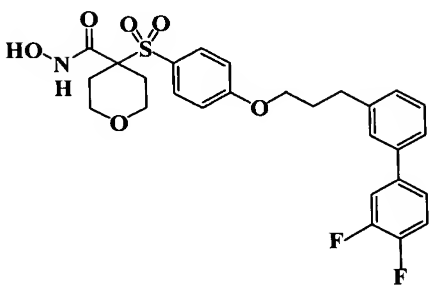

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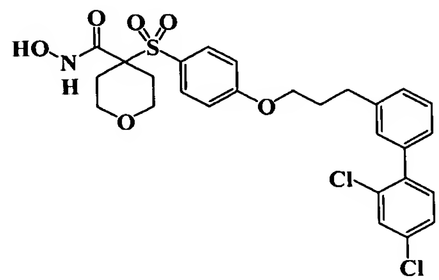

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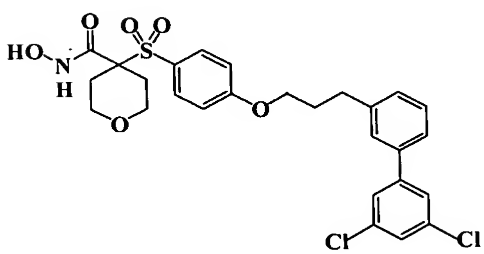
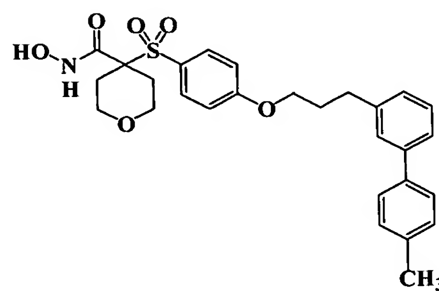
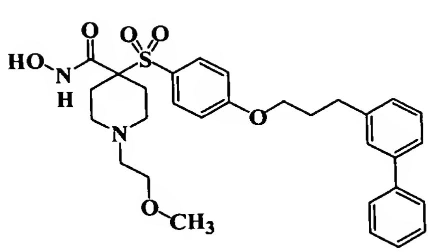


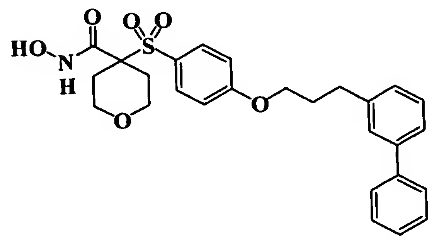
IIIB-65



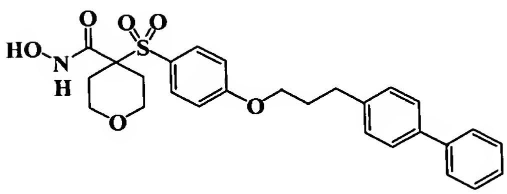
IIIB-66



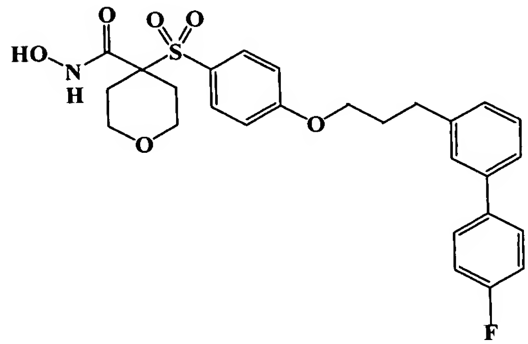
IIIB-67



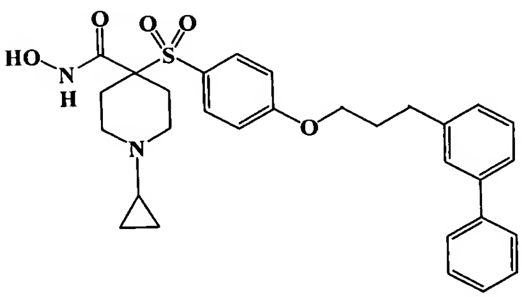
IIIB-68



IIIB-69

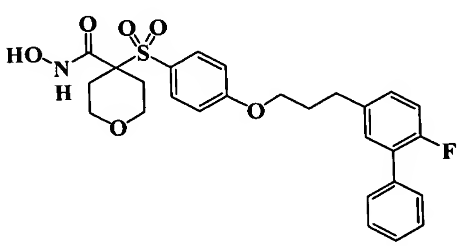


IIIB-70

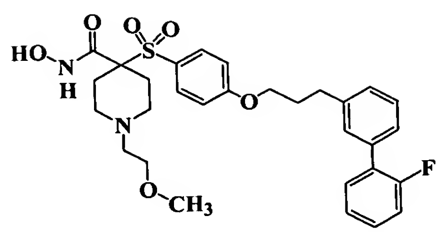


IIIB-71

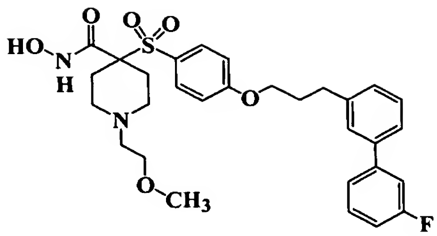
Other such compounds include, for example:



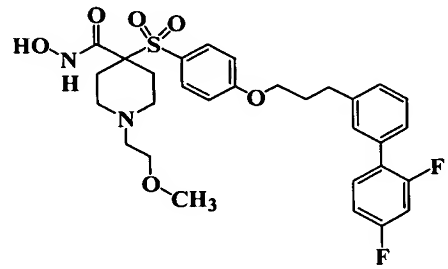
IIIB-72



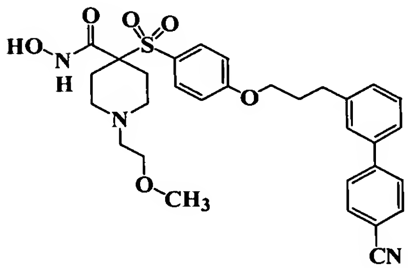
IIIB-73



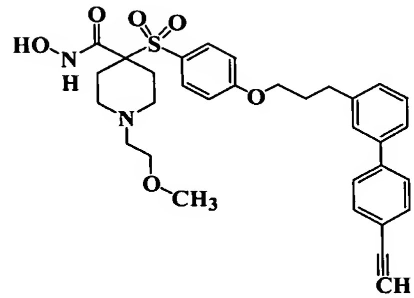
IIIB-74



IIIB-75



IIIB-76



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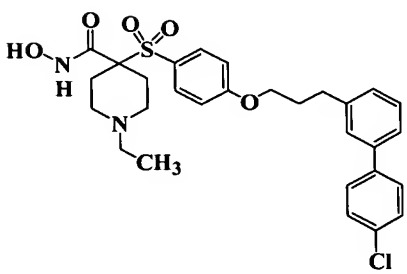
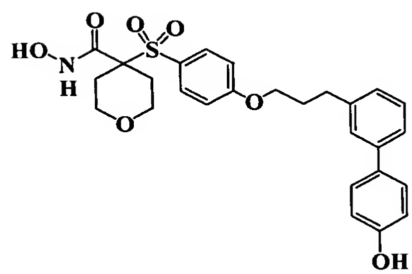
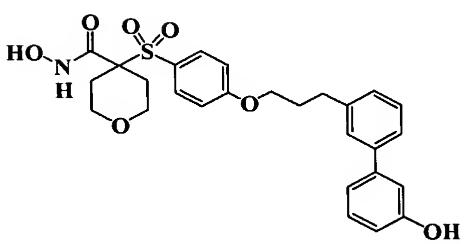


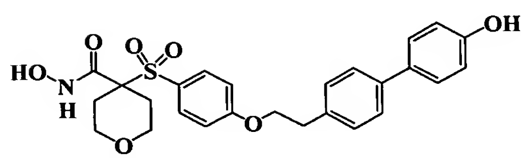
IIIB-78



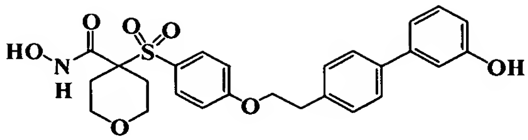
IIIB-79



IIIB-80



IIIB-81



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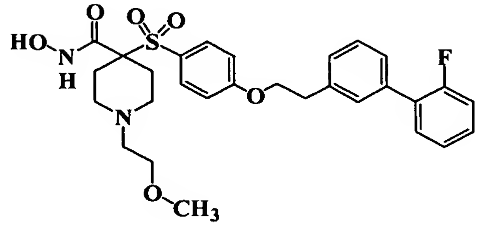
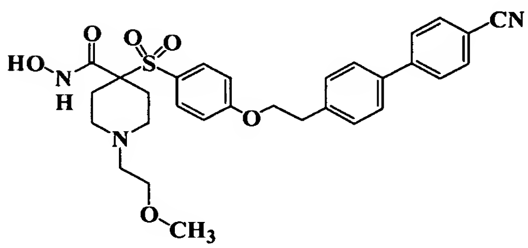
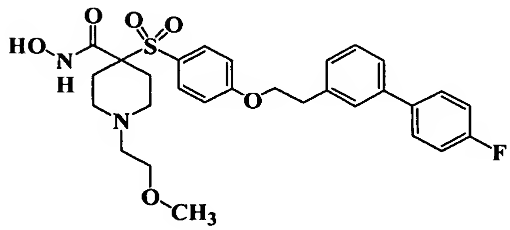


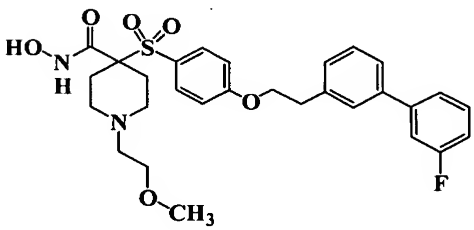
IIIB-83



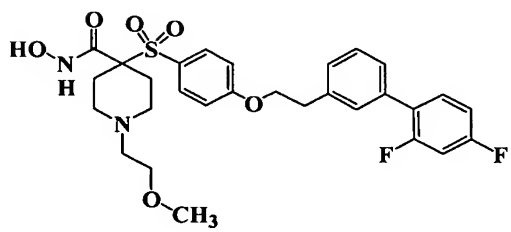
IIIB-84



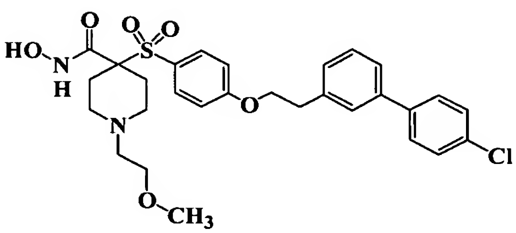
IIIB-85



IIIB-86



IIIB-87



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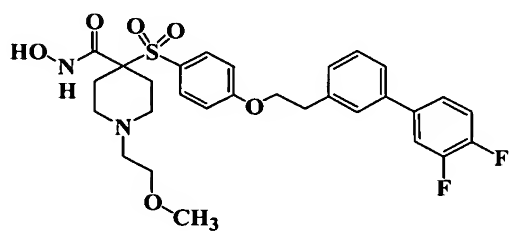

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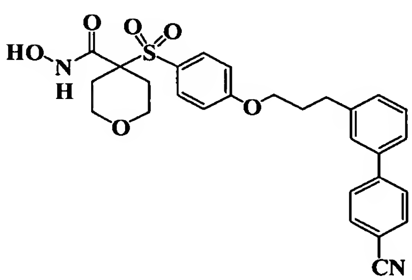

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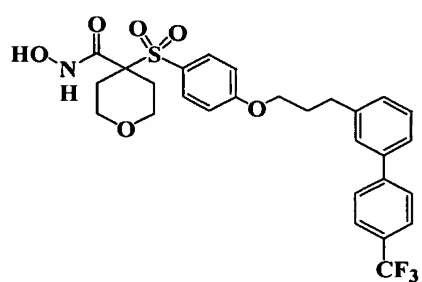

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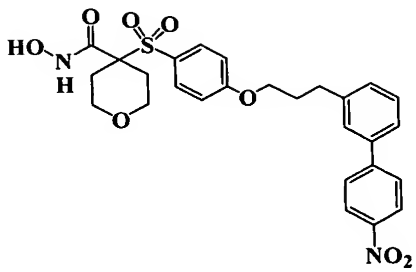

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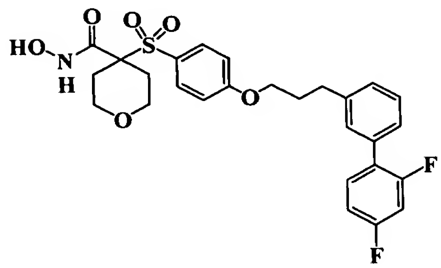

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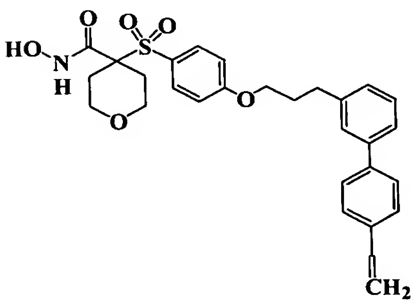

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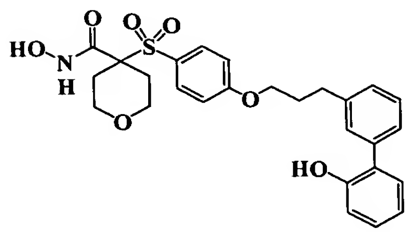

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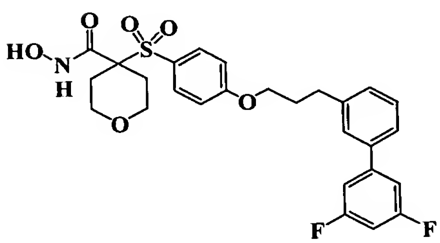

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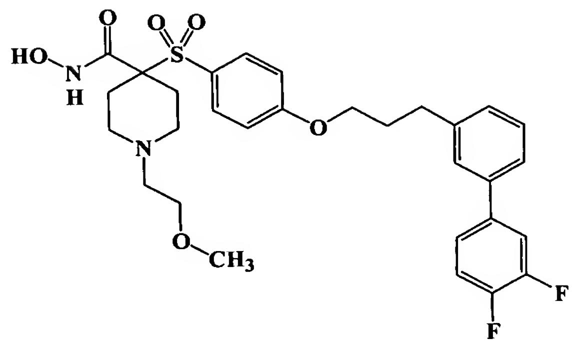

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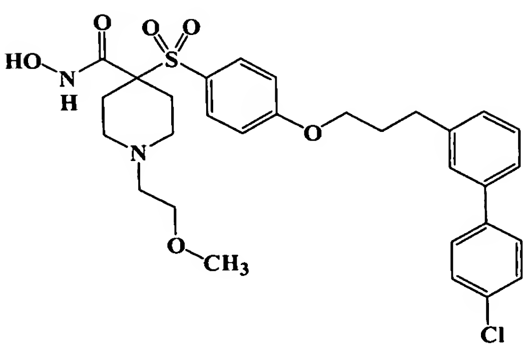
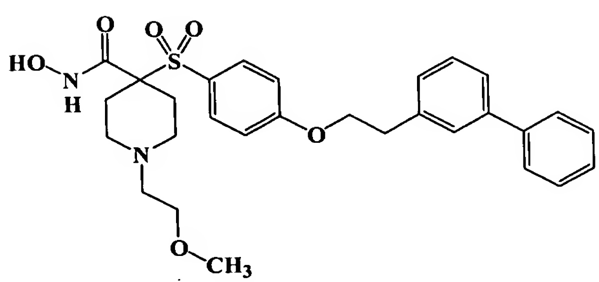
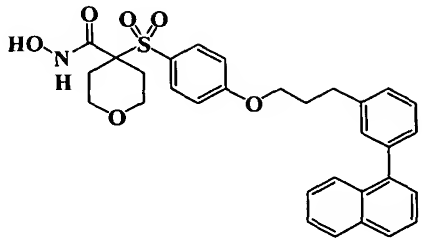


IIIB-98

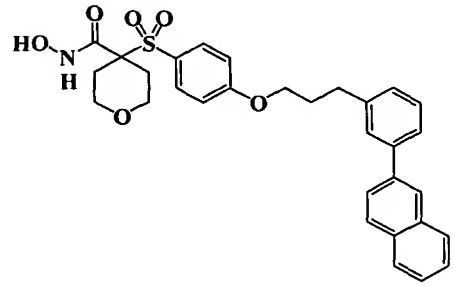


IIIB-99

[220] In other preferred embodiments, E^5 is optionally-substituted naphthalenyl. Such compounds include, for example:



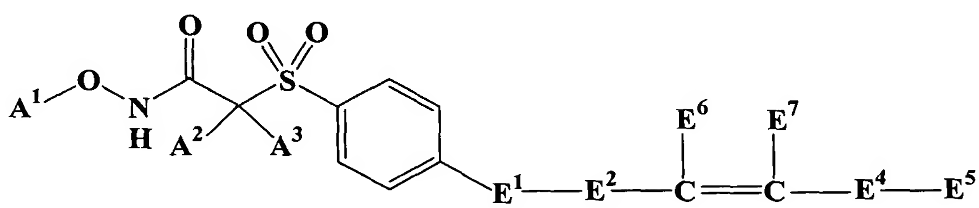
IIIB-100



IIIB-101

Preferred Embodiment No. 3

[221] In some embodiments of this invention, the compound has a structure corresponding to Formula IV:



IV

[222] A^1, A^2, and A^3 are as defined above for Formula I.

[223] E^1 is s -O-, -S(O)$_2$-, -S(O)-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-.

[224] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[225] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[226] In some preferred embodiments, E^2 is C_1-C_6-alkyl, cycloalkyl, C_1-C_6-alkylcycloalkyl, cycloalkyl-C_1-C_6-alkyl, or C_1-C_6-alkylcycloalkyl-C_1-C_6-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_2-alkyl, and halo-C_1-C_2-alkyl.

[227] In some preferred embodiments, E^2 is C_1-C_6-alkyl, cycloalkyl, C_1-C_6-alkylcycloalkyl, cycloalkyl-C_1-C_6-alkyl, or C_1-C_6-alkylcycloalkyl-C_1-C_6-alkyl. Any member of this group optionally is substituted with one or more C_1-C_2-alkyl.

[228] E^4 is a bond or alkyl. The alkyl optionally is substituted.

[229] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, or halo-C_1-C_{20}-alkyl.

[230] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or halo-C_1-C_3-alkyl.

[231] In some preferred embodiments, E^4 is a bond or C_1-C_3-alkyl.

[232] In some preferred embodiments, E^4 is a bond.

[233] E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[234] In some preferred embodiments, E^5 is C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, -$N(R^7)(R^8)$, -$C(O)(R^9)$, -S-R^7, -$S(O)_2$-R^7, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl.

[235] In some preferred embodiments, E^5 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, -$N(R^7)(R^8)$, -$C(O)(R^9)$, -S-R^7, -$S(O)_2$-R^7, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl.

[236] E^6 is -H, halogen, or alkyl. The alkyl optionally is substituted.

[237] In some preferred embodiments, E^6 is -H, halogen, or C_1-C_8-alkyl. The C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[238] In some preferred embodiments, E^6 is -H, halogen, or C_1-C_6-alkyl. The C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[239] E^7 is -H, alkyl, alkenyl, alkynyl, -S(O)$_2$-R^3, -NO_2, -C(O)-N(R^3)(R^4), -(C)(OR^3), carbocyclyl, carbocyclylalkyl, alkoxycarbocyclyl, -CN, -C=N-OH, or -C=NH. The alkyl, alkenyl, alkynyl, carbocyclyl, carbocyclylalkyl, and alkoxycarbocyclyl optionally are substituted.

[240] In some preferred embodiments, E^7 is -H, C_1-C_8-alkyl, C_1-C_8-alkenyl, C_1-C_8-alkynyl, -S(O)$_2$-R^3, -NO_2, -C(O)-N(R^3)(R^4), -(C)(OR^3), carbocyclyl, carbocycyl-C_1-C_8-alkyl, C_1-C_8-alkoxycarbocyclyl, -CN, -C=N-OH, or -C=NH. The C_1-C_6-alkyl, C_1-C_8-alkenyl, C_1-C_8-alkynyl, carbocyclyl, carbocycyl-C_1-C_8-alkyl, or C_1-C_8-alkoxycarbocyclyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[241] In some preferred embodiments, E^7 is -H, C_1-C_6-alkyl, C_1-C_6-alkenyl, C_1-C_6-alkynyl, -S(O)$_2$-R^3, -NO_2, -C(O)-N(R^3)(R^4), -(C)(OR^3), carbocyclyl, carbocycyl-C_1-C_6-alkyl, C_1-C_6-alkoxycarbocyclyl, -CN, -C=N-OH, or -C=NH. The C_1-C_6-alkyl, C_1-C_6-alkenyl, C_1-C_6-alkynyl, carbocyclyl, carbocycyl-C_1-C_6-alkyl, or C_1-C_6-alkoxycarbocyclyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[242] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^4, E^5, E^6, or E^7.

[243] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl.

[244] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[245] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_6-alkyl.

[246] R^3 and R^4 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group optionally is substituted.

[247] In some preferred embodiments, R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[248] In some preferred embodiments, R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[249] R^7 and R^8 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[250] In some preferred embodiments, R^7 and R^8 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

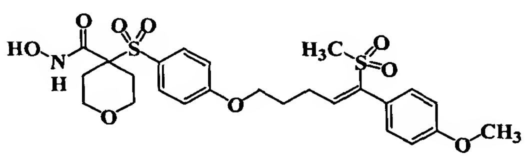
[251] R^9 is -H, C_1-C_8-alkyl, -O-R^{10}, -N(R^{10})(R^{11}), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[252] In some preferred embodiments, R^9 is -H, C_1-C_6-alkyl, -O-R^{10}, -N(R^{10})(R^{11}), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[253] R^{10} and R^{11} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[254] In some preferred embodiments, R^{10} and R^{11} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[255] In some preferred embodiments, E^5 is optionally-substituted carbocyclyl or optionally-substituted heterocyclyl. For example, in some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



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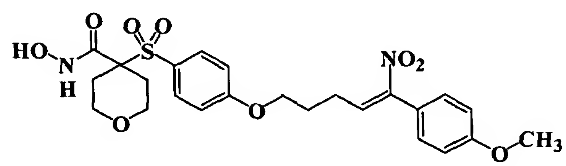

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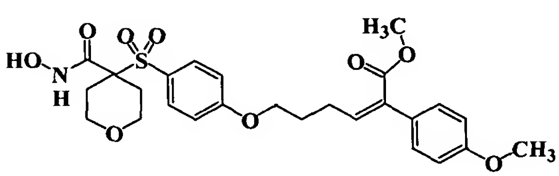

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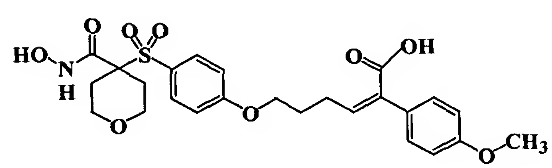

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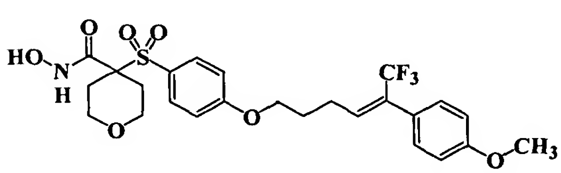
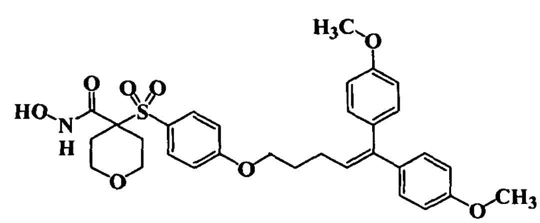
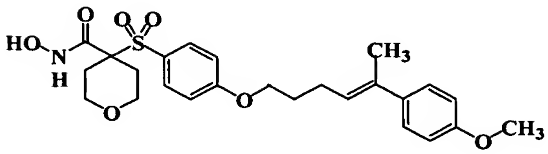


IV-5



IV-6



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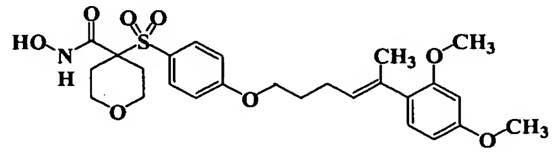

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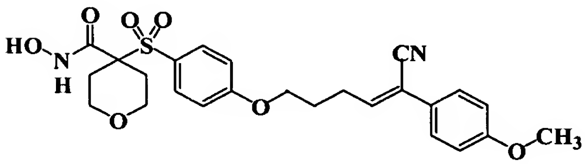

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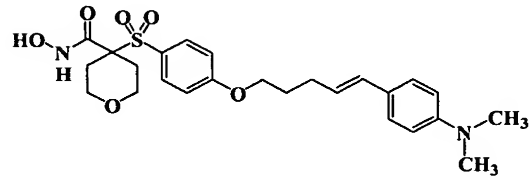

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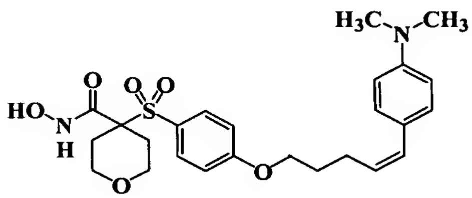

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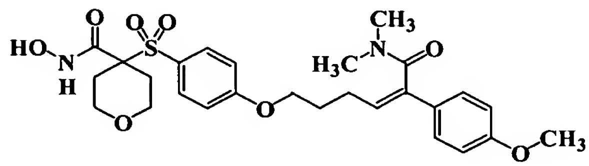

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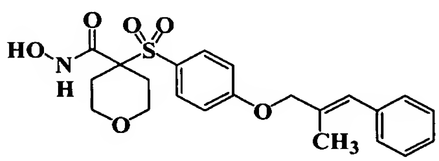

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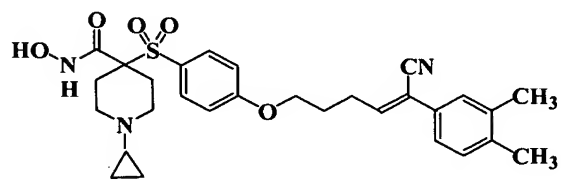

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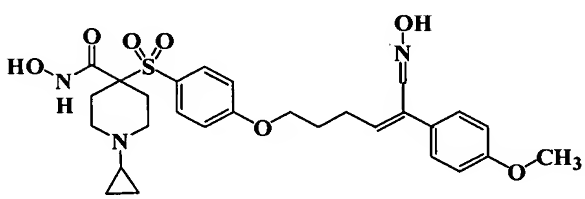

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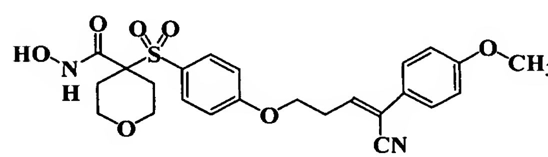
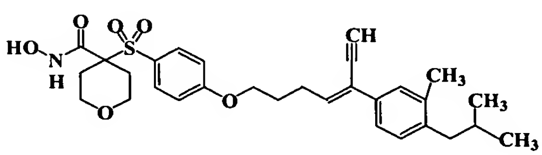
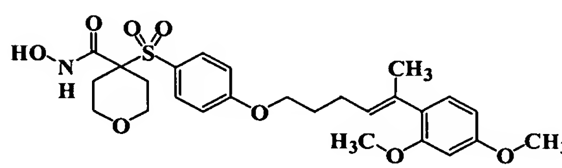


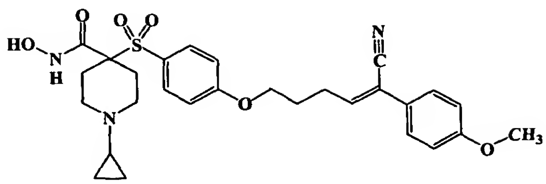
IV-16



IV-17



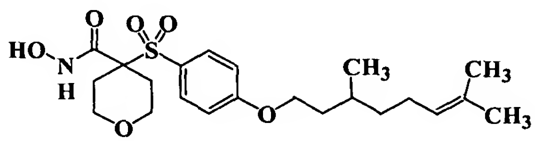
IV-18



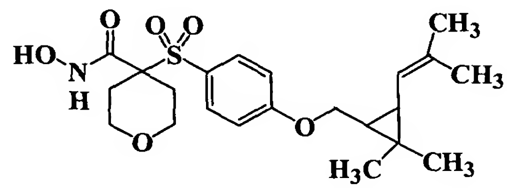
IV-19

[256] In some preferred embodiments, E^5 is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, or C_1-C_6-alkoxy-C_1-C_6-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN.

[257] In some preferred embodiments, E^5 is optionally-substituted C_1-C_6-alkyl, with the C_1-C_6-alkyl often being more preferably unsubstituted. Such compounds include, for example:



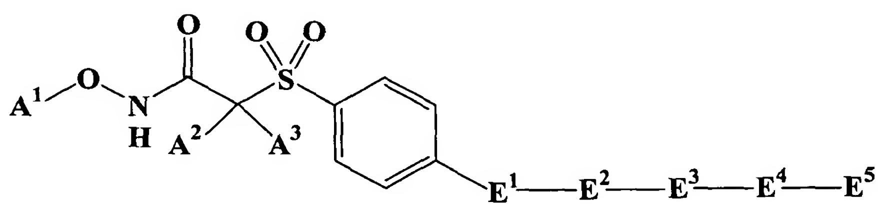
IV-20



IV-21

Preferred Embodiment No. 4

[258] In some embodiments of this invention, the compound has a structure corresponding to Formula V:



V

[259] A^1, A^2, and A^3 are as defined above for Formula I.

[260] E^1 is -O-, $-S(O)_2-$, -S(O)-, $-N(R^3)-$, $-C(O)-N(R^3)-$, $-N(R^3)-C(O)-$, or $-C(R^1)(R^2)-$.

[261] E^2 is a bond, alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Except where the member is a bond, any member of such group optionally is substituted.

[262] In some preferred embodiments, E^2 is a bond, C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group (except for the bond) optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[263] In some preferred embodiments, E^2 is a bond, C_1-C_6-alkyl, or halo-C_1-C_6-alkyl.

[264] In some preferred embodiments E^2 is a bond or C_1-C_6-alkyl.

[265] E^3 is carbonylpyrrollidinyl. The carbonylpyrrollidinyl optionally is substituted.

[266] In some preferred embodiments, E^3 is carbonylpyrrollidinyl wherein the carbonylpyrrollidinyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[267] E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

[268] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, or halo-C_2-C_{20}-alkenyl.

[269] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, halo-C_1-C_3-alkyl, C_2-C_3-alkenyl, or halo-C_2-C_3-alkenyl.

[270] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl.

[271] In some preferred embodiments, E^4 is a bond.

[272] E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[273] In some preferred embodiments, E^5 is C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The

carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl.

[274] In some preferred embodiments, E^5 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[275] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

[276] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_6-alkyl.

[277] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[278] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_6-alkyl.

[279] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[280] In some preferred embodiments, R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

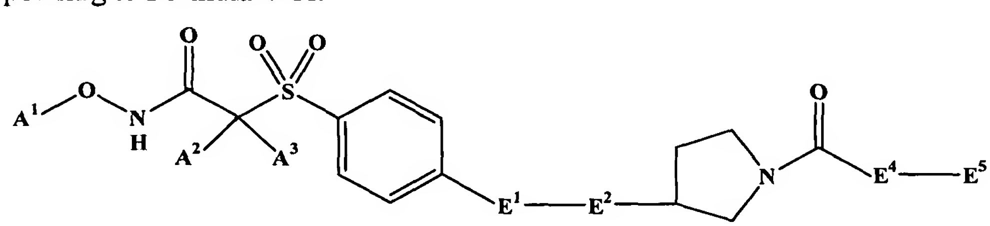
[281] R^7 is -H, C_1-C_8-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[282] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[283] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

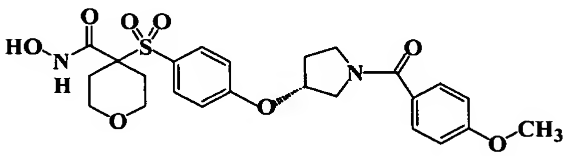
[284] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[285] In some preferred embodiments, the compound has a structure corresponding to Formula V-A:

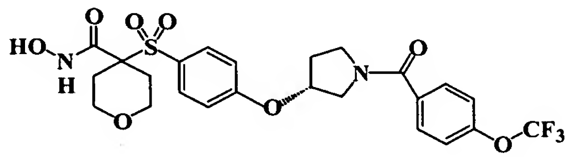


V-A

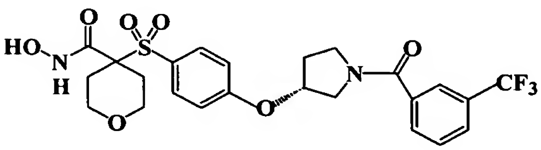
[286] In some preferred embodiments, E^5 is optionally-substituted carbocyclyl or optionally substituted heterocyclyl. For example, in some such embodiments, E^5 is optionally substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



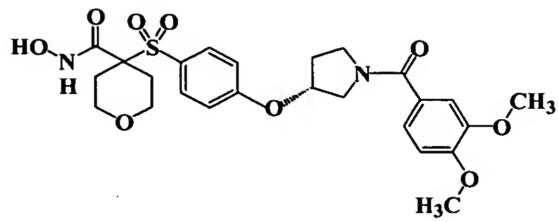
V-1



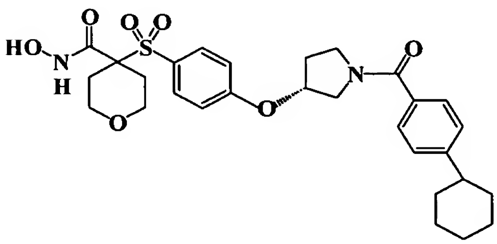
V-2



V-3

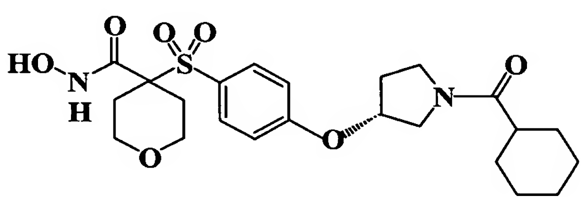


V-4



V-5

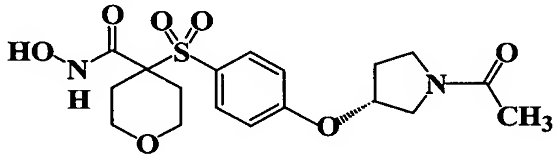
[287] In some preferred embodiments, E^5 is optionally-substituted C_5-C_6-cycloalkyl. Such compounds include, for example:



V-6

[288] In some preferred embodiments, E^5 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, or C_1-C_8-alkoxy-C_1-C_8-alkyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN.

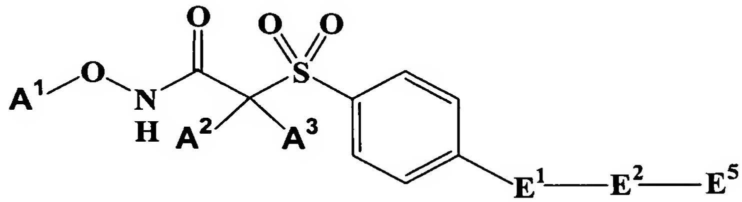
[289] In some preferred embodiments, E^5 is optionally-substituted C_1-C_8-alkyl, with C_1-C_8-alkyl often being more preferred. Such compounds include, for example:



V-7

Preferred Embodiment No. 5

[290] In some embodiments of this invention, the compound has a structure corresponding to Formula VI:



VI

[291] A^1, A^2, and A^3 are as defined above for Formula I.

[292] E^1 is -O-, -S(O)$_2$-, -S(O)-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-.

[293] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, alkyl, and haloalkyl.

[294] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[295] In some preferred embodiments, E^2 is C_1-C_6-alkyl, cycloalkyl, C_1-C_6-alkylcycloalkyl, cycloalkyl-C_1-C_6-alkyl, or C_1-C_6-alkylcycloalkyl-C_1-C_6-alkyl. Any member of this group optionally is substituted with one or more substituents

independently selected from the group consisting of halogen, C_1-C_2-alkyl, and halo-C_1-C_2-alkyl.

[296] In some preferred embodiments, E^2 is C_1-C_6-alkyl, cycloalkyl, C_1-C_6-alkylcycloalkyl, cycloalkyl-C_1-C_6-alkyl, or C_1-C_6-alkylcycloalkyl-C_1-C_6-alkyl. Any member of this group optionally is substituted with one or more C_1-C_2-alkyl.

[297] E^5 is alkyl, alkenyl, alkynyl, cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, or cyclohexadienyl. Here, the cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, and cyclohexadienyl optionally are substituted. The alkyl, alkenyl, and alkynyl (a) contain at least 4 carbon atoms, and (b) optionally are substituted with one or more substituents selected from the group consisting of -OH, -NO_2, -CN, and halogen.

[298] In some preferred embodiments, E^5 is C_4-C_{20}-alkyl, C_4-C_{20}-alkenyl, C_4-C_{20}-alkynyl, cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, or cyclohexadienyl. The C_4-C_{20}-alkyl, C_4-C_{20}-alkenyl, and C_4-C_{20}-alkynyl optionally are substituted with one or more substituents independently selected from the group consisting of -OH, -NO_2, -CN, and halogen. The cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, and cyclohexadienyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, -N(R^5)(R^6), -C(O)(R^7), -S-R^5, -S(O)$_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl.

[299] In some preferred embodiments, E^5 is C_4-C_8-alkyl, C_4-C_8-alkenyl, C_4-C_8-alkynyl, cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, or cyclohexadienyl. The C_4-C_8-alkyl, C_4-C_8-alkenyl, and C_4-C_8-alkynyl optionally are substituted with one or more substituents independently selected from the group consisting of -OH, -NO_2, -CN, and halogen. The cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, and cyclohexadienyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -N(R^5)(R^6), -C(O)(R^7), -S-R^5, -S(O)$_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[300] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^5.

[301] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl.

[302] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[303] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_6-alkyl.

[304] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[305] In some preferred embodiments, R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

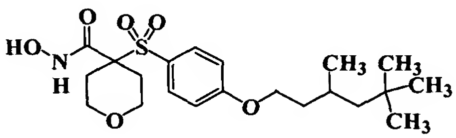
[306] R^7 is -H, C_1-C_8-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[307] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

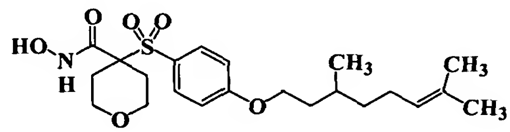
[308] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[309] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

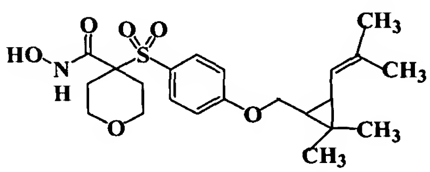
[310] In some preferred embodiments, E^5 is C_4-C_8-alkyl, C_4-C_8-alkenyl, or C_4-C_8-alkynyl. The C_4-C_8-alkyl, C_4-C_8-alkenyl, and C_4-C_8-alkynyl optionally are substituted with one or more substituents independently selected from the group consisting of -OH, $-NO_2$, -CN, and halogen. Such compounds include, for example:



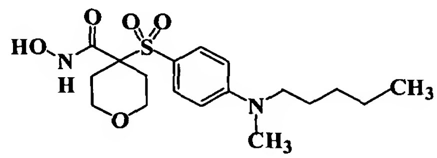
VI-1



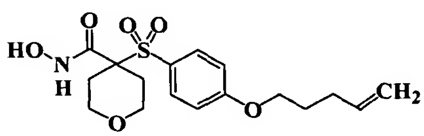
VI-2



VI-3

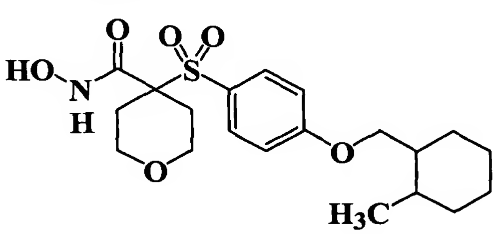


VI-4

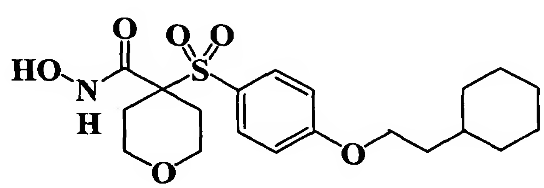


VI-5

[311] In some preferred embodiments, E^5 is optionally-substituted carbocyclyl. In some such embodiments, E^5 is optionally-substituted C_5-C_6-cycloalkyl. Such compounds include, for example:

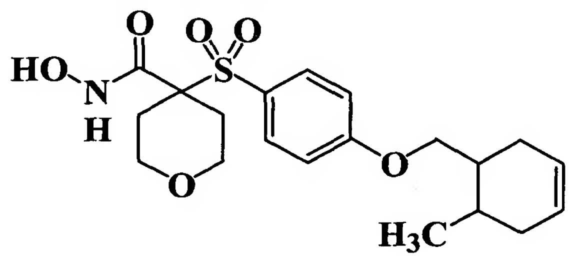


VI-6



VI-7

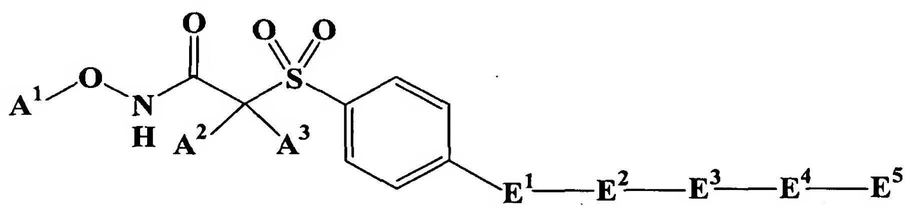
In other such embodiments, E^5 is an optionally-substituted, partially-saturated carbocyclyl selected from the group consisting of cyclopentenyl, cyclopentadienyl, cyclohexenyl, and cyclohexadienyl. Such compounds include, for example:



VI-8

Preferred Embodiment No. 6

[312] In some embodiments of this invention, the compound has a structure corresponding to Formula VII:



VII

[313] A^1, A^2, and A^3 are as defined above for Formula I.

[314] E^1 is -O-, -S(O)$_2$-, -S(O)-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-.

[315] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[316] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

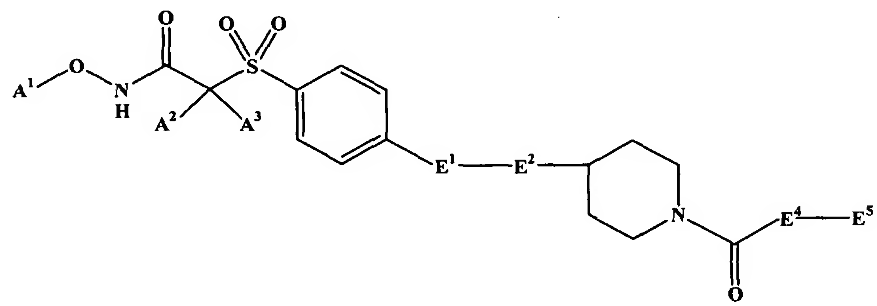
[317] In some preferred embodiments, E^2 is C_1-C_6-alkyl optionally substituted with one or more halogen.

[318] In some preferred embodiments, E^2 is C_1-C_6-alkyl.

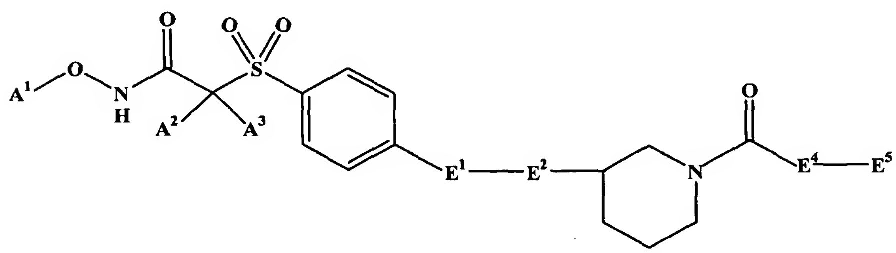
[319] E^3 is carbonylpiperidinyl. The carbonylpiperidinyl optionally is substituted.

[320] In some preferred embodiments, E^3 is carbonylpiperidinyl wherein the carbonylpiperidinyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[321] In some preferred embodiments, the compound has a structure corresponding to one of the following formulas:



VII-A



VII-B

[322] E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

[323] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, or halo-C_2-C_{20}-alkenyl.

[324] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, halo-C_1-C_3-alkyl, C_2-C_3-alkenyl, or halo-C_2-C_3-alkenyl.

[325] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl.

[326] In some preferred embodiments, E^4 is a bond.

[327] E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[328] In some preferred embodiments, E^5 is C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, -N(R^5)(R^6), -C(O)(R^7), -S-R^5, -S(O)$_2$-R^5, carbocyclyl, halocarbocyclyl, and carbocyclyl-C_1-C_8-alkyl.

[329] In some preferred embodiments, E^5 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, or heterocyclyl. Here, the C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -N(R^5)(R^6), -C(O)(R^7), -S-R^5, -S(O)$_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[330] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

[331] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[332] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[333] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_6-alkyl.

[334] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and

heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[335] In some preferred embodiments, R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

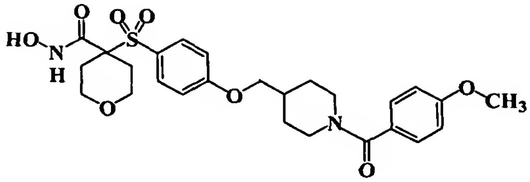
[336] R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[337] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

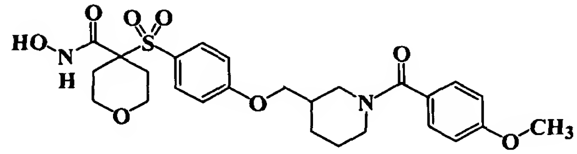
[338] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[339] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[340] In some preferred embodiments, E^5 is optionally-substituted carbocyclyl or optionally substituted heterocyclyl. In some such embodiments, E^5 is optionally-substituted aryl, often preferably optionally-substituted phenyl. Such compounds include, for example:



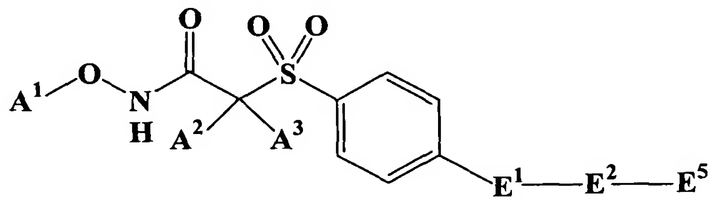
VII-1



VII-2

Preferred Embodiment No. 7

[341] In some embodiments of this invention, the compound has a structure corresponding to Formula VIII:



VIII

[342] A^1, A^2, and A^3 are as defined above for Formula I.

[343] E^1 is -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

[344] E^2 forms a link of at least 3 carbon atoms between E^1 and E^5. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[345] In some preferred embodiments, E^2 is C_3-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkyl-cycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkyl-cycloalkyl-C_1-C_{10}-alkyl. Any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[346] In some preferred embodiments, E^2 is C_3-C_6-alkyl optionally substituted with one or more halogen.

[347] In some preferred embodiments, E^2 is C_3-C_6-alkyl.

[348] E^5 is optionally-substituted heterocyclyl, optionally-substituted fused-ring carbocyclyl, or substituted single-ring carbocyclyl.

[349] In some preferred embodiments, E^5 is single-ring carbocyclyl, fused-ring carbocyclyl, or heterocyclyl.

[350] Here, the single-ring carbocyclyl is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl. The single-ring carbocyclyl also optionally is substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_5-C_6-cycloalkyl or halo-C_5-C_6-cycloalkyl.

[351] In some preferred embodiments, the single-ring carbocyclyl is substituted with one or more substituents independently selected from the group consisting of and halogen, -OH, $-NO_2$, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl. The single-ring carbocyclyl also optionally is substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_5-C_6-cycloalkyl or halo-C_5-C_6-cycloalkyl.

[352] The heterocyclyl and fused-ring carbocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of and halogen, -OH, $-NO_2$, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, and carbocyclyl-C_1-C_6-alkyl. The heterocyclyl and fused-ring carbocyclyl also optionally are substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_5-C_6-cycloalkyl or halo-C_5-C_6-cycloalkyl.

[353] In some preferred embodiments, the heterocyclyl and fused-ring carbocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of and halogen, -OH, $-NO_2$, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl,

halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -N(R^5)(R^6), -C(O)(R^7), -S-R^5, -S(O)$_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl. The heterocyclyl and fused-ring carbocyclyl also optionally are substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_5-C_6-cycloalkyl or halo-C_5-C_6-cycloalkyl.

[354] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^5.

[355] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl.

[356] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[357] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_6-alkyl.

[358] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[359] In some preferred embodiments, R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[360] R^7 is -H, C_1-C_8-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[361] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl,

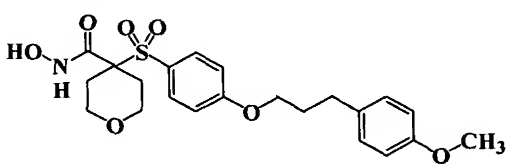
carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[362] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

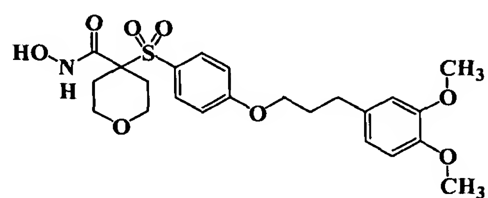
[363] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[364] In some preferred embodiments, E^5 is a substituted single-ring carbocyclyl. E^5 may be, for example a substituted single-ring carbocyclyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl.

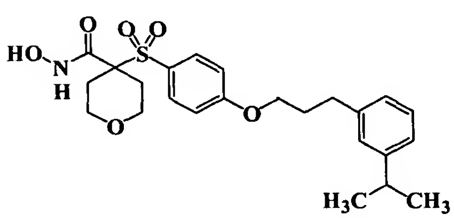
[365] In some preferred embodiments, E^5 is substituted phenyl. Such compounds include, for example:



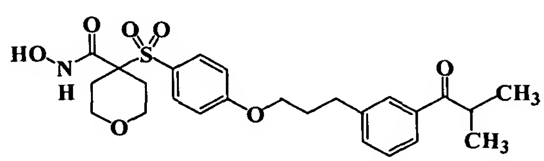
VIII-1



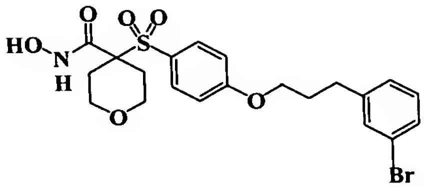
VIII-2



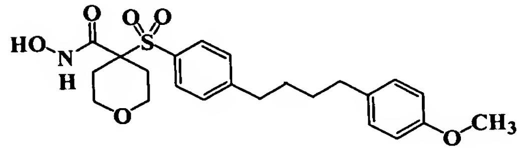
VIII-3



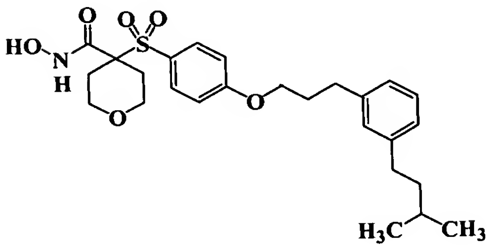
VIII-4



VIII-5

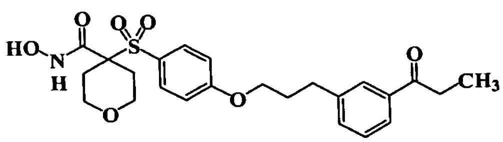


VIII-6

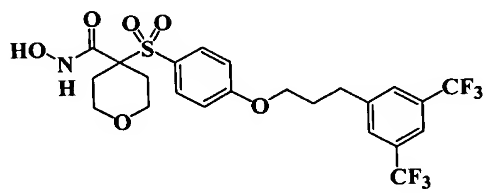


VIII-7

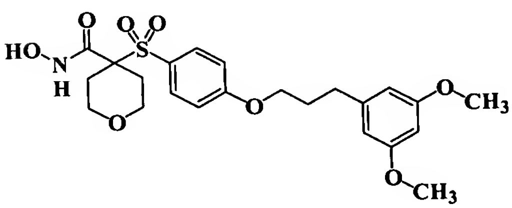
Such compounds also include, for example:



VIII-8



VIII-9



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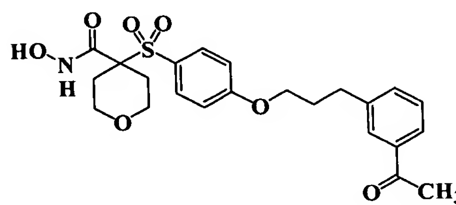
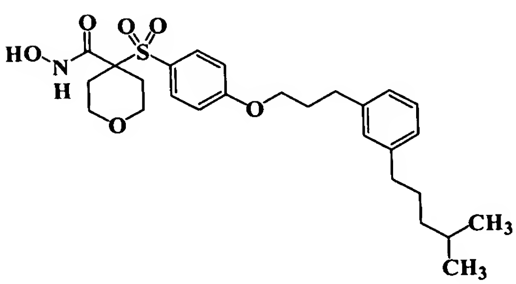
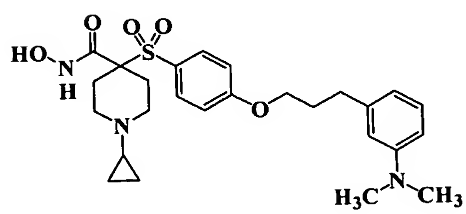


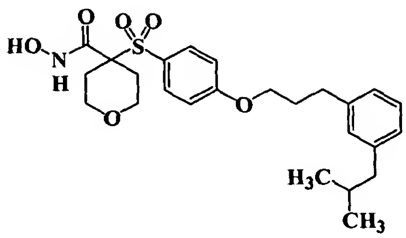
VIII-11



VIII-12



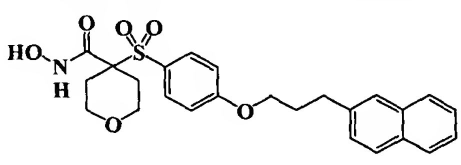
VIII-13



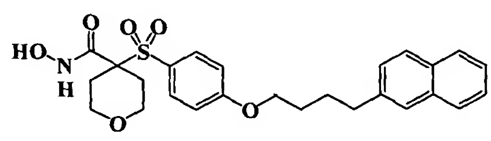
VIII-14

[366] In some preferred embodiments, E^5 is optionally-substituted fused-ring carbocyclyl. E^5 may be, for example, optionally-substituted fused-ring carbocyclyl selected from the group consisting of naphthalenyl, tetrahydronaphthalenyl, indenyl, isoindenyl, indanyl, bicyclodecanyl, anthracenyl, phenanthrene, benzonaphthenyl, fluoreneyl, decalinyl, and norpinanyl.

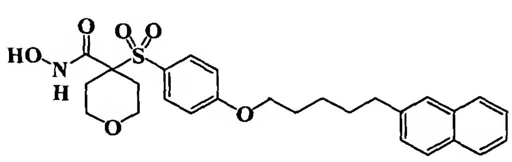
[367] In some preferred embodiments, E^5 is optionally-substituted naphthalenyl. Such compounds include, for example:



VIII-15



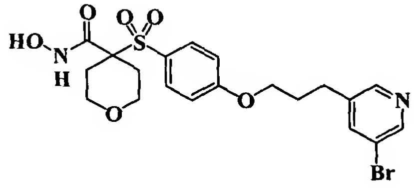
VIII-16



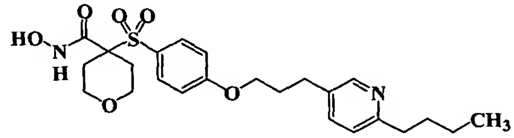
VIII-17

[368] In some preferred embodiments, E^5 is optionally-substituted, single-ring heterocyclyl.

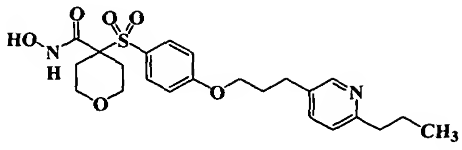
[369] In some preferred embodiments, E^5 is an optionally-substituted pyridinyl. Such compounds include, for example:



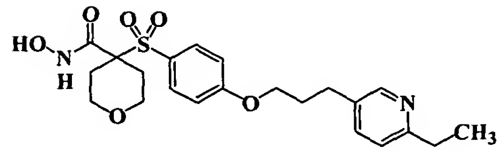
VIII-18



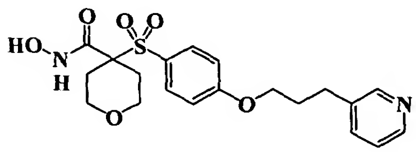
VIII-19



VIII-20

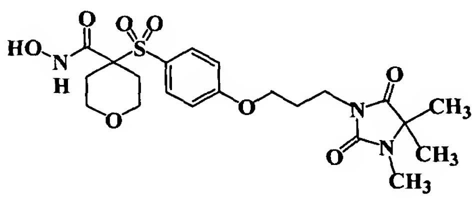


VIII-21

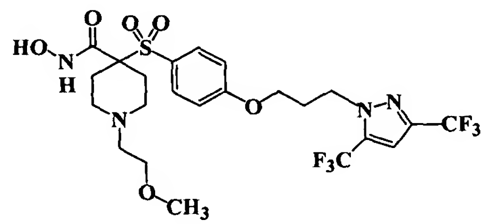


VIII-22

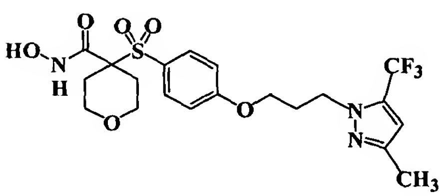
[370] In some preferred embodiments, E^5 is an optionally-substituted heterocyclyl selected from the group consisting of imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, and pyrazolidinyl. Such compounds include, for example:



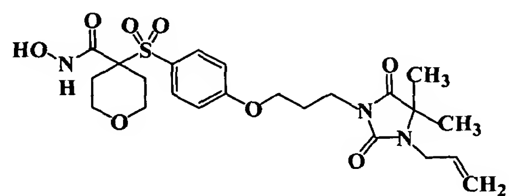
VIII-23



VIII-24



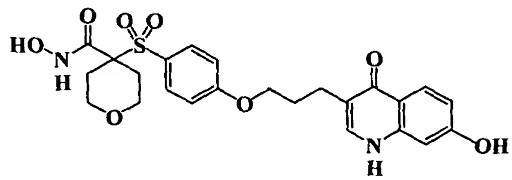
VIII-25



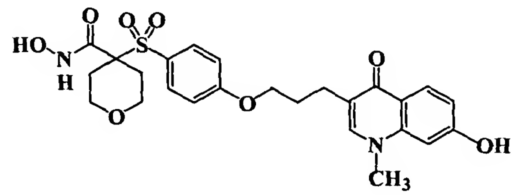
VIII-26

[371] In some preferred embodiments, E^5 is optionally-substituted fused-ring heterocyclyl. E^5 may be, for example, an optionally-substituted fused-ring heterocyclyl selected from the group consisting of indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl,

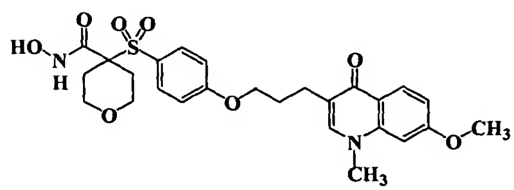
benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinolinyl , carbazolyl, xanthenyl, and acridinyl. Compounds wherein E^5 is an optionally-substituted fused-ring heterocyclyl include, for example:



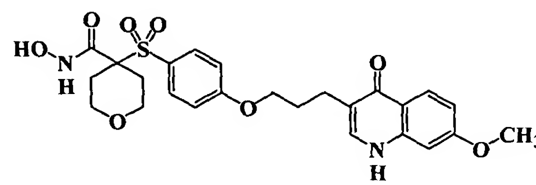
VIII-27



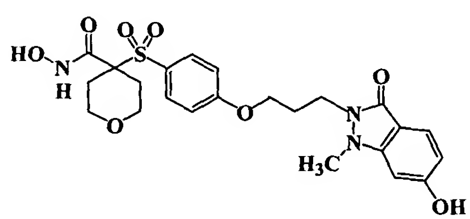
VIII-28



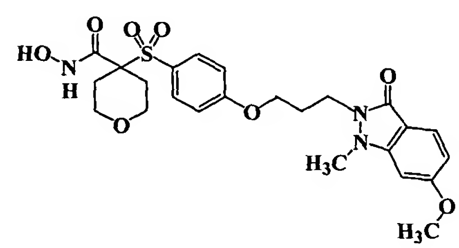
VIII-29



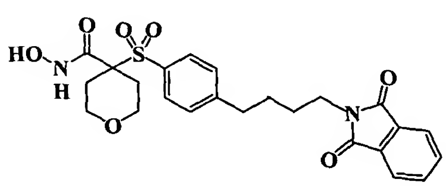
VIII-30



VIII-31



VIII-32



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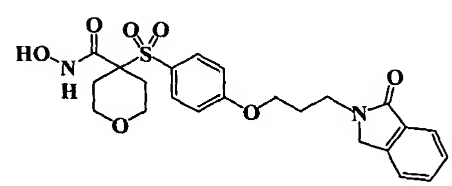
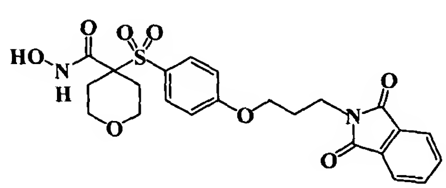
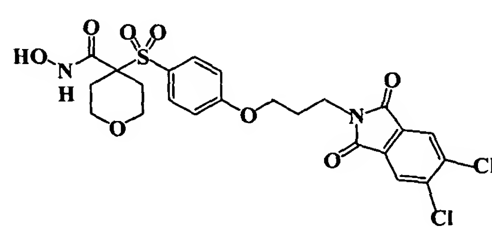


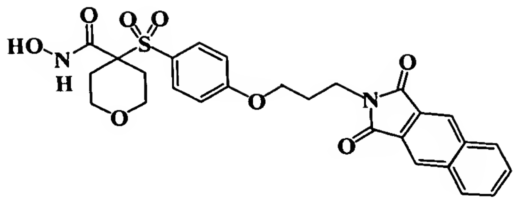
VIII-34



VIII-35



VIII-36



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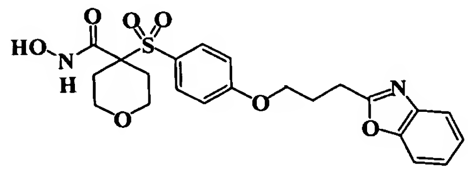
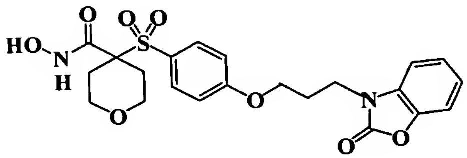
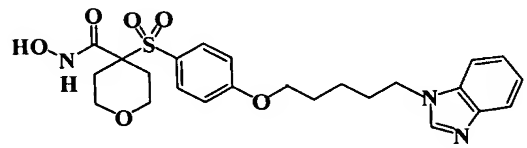


VIII-38

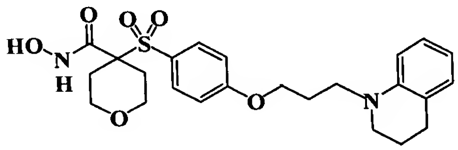


VIII-39

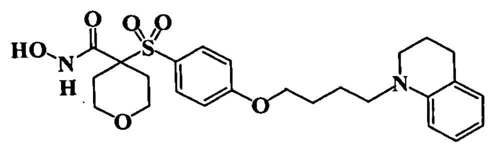


VIII-40

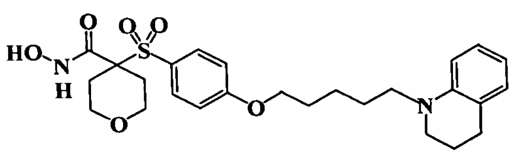
[372] In some preferred embodiments, E^5 is optionally-substituted tetrahydroisoquinolinyl . Such compounds include, for example:



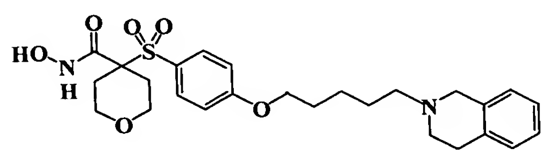
VIII-41



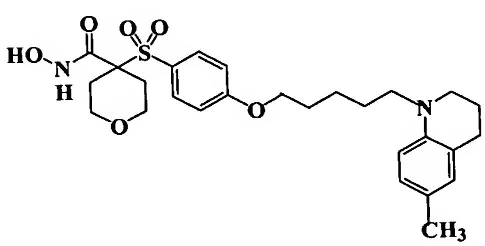
VIII-42



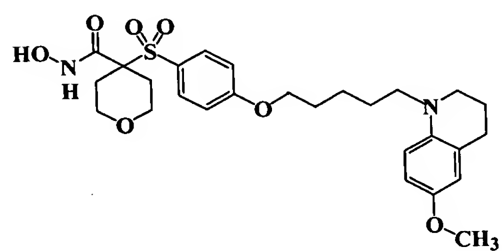
VIII-43



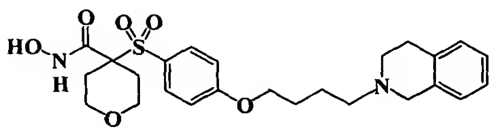
VIII-44



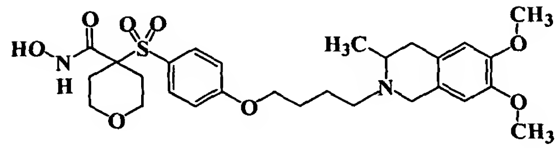
VIII-45



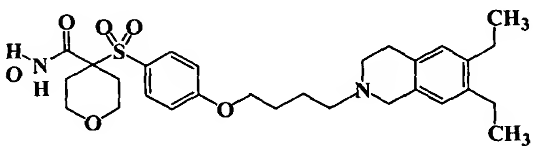
VIII-46



VIII-47

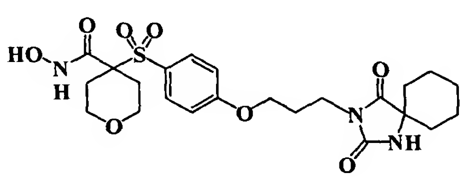


VIII-48



VIII-49

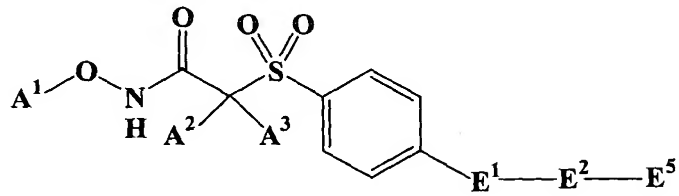
[373] In some preferred embodiments, E^5 is heterocyclyl that is substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_5-C_6-cycloalkyl or halo-C_5-C_6-cycloalkyl. This heterocyclyl also optionally is substituted with one or more substituents independently selected from the group consisting of and halogen, -OH, $-NO_2$, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl. The heterocyclyl that is substituted may be, for example, selected from the group consisting of dihydrofuranyl, tetrahydrofuranyl, dihydrothiophenyl, tetrahydrothiophenyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, dithiolyl, oxathiolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, oxathiolanyl, pyranyl, dihydropyranyl, piperidinyl, piperazinyl, and morpholinyl. Such compounds include, for example:



VIII-50

Preferred Embodiment No. 8

[374] In some embodiments of this invention, the compound has a structure corresponding to Formula IX:



IX

[375] A^1, A^2, and A^3 are as defined above for Formula I.

[376] E^1 is -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

[377] E^2 forms a link of at least 4 carbon atoms between E^1 and E^5. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[378] In some preferred embodiments, E^2 is C_4-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkyl-cycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkyl-cycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[379] In some preferred embodiments, E^2 is C_4-C_6-alkyl optionally substituted with one or more halogen.

[380] In some preferred embodiments, E^2 is C_4-C_6-alkyl.

[381] E^5 is -OH or optionally-substituted carbocyclyl.

[382] In some preferred embodiments, E^5 is -OH or carbocyclyl wherein the carbocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of and halogen, -OH, $-NO_2$, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl. The carbocyclyl also optionally is substituted with two

C_1-C_8-alkyl or halo-C_1-C_8-alkyl groups on the same atom that form a C_5-C_6-cycloalkyl or C_5-C_6-halocycloalkyl.

[383] In some preferred embodiments, E^5 is -OH or carbocyclyl wherein the carbocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of and halogen, -OH, $-NO_2$, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[384] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^5.

[385] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl.

[386] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[387] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_6-alkyl.

[388] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[389] In some preferred embodiments, R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

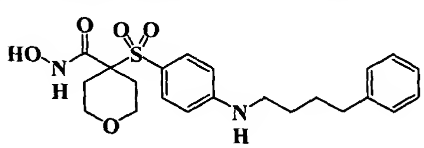
[390] R^7 is -H, C_1-C_8-alkyl, $-O-R^8$, $-N(R^8)(R^9)$, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[391] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

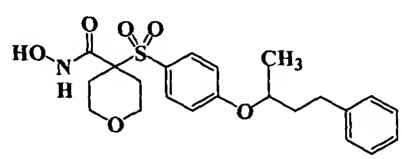
[392] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[393] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen. Such compounds include, for example:

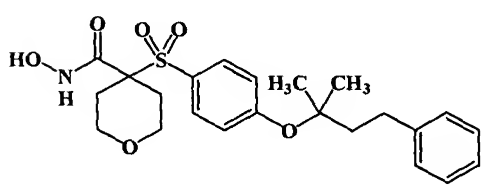
[394] In some preferred embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



IX-1

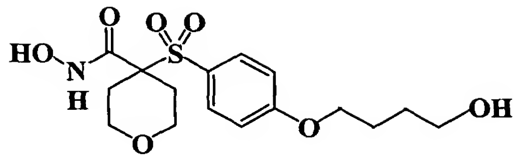


IX-2

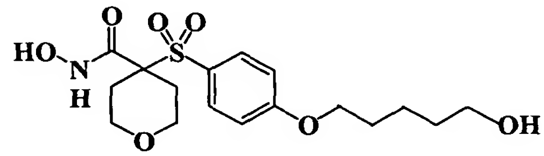


IX-3

[395] In some preferred embodiments, E^5 is -OH. Such compounds include, for example:



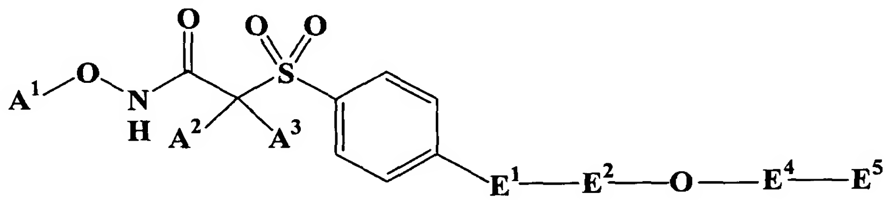
IX-4



IX-5

Preferred Embodiment No. 9

[396] In some embodiments of this invention, the compound has a structure corresponding to Formula X:



X

[397] A^1, A^2, and A^3 are as defined above for Formula I.

[398] E^1 is -S(O)$_2$-, -S(O)-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-.

[399] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[400] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, C_1-C_6-halo-alkyl.

[401] In some preferred embodiments, E^2 is C_2-C_6-alkyl optionally substituted with one or more halogen.

[402] In some preferred embodiments, E^2 is C_2-C_6-alkyl.

[403] E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

[404] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, or halo-C_2-C_{20}-alkenyl.

[405] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, halo-C_1-C_3-alkyl, C_2-C_3-alkenyl, or halo-C_2-C_3-alkenyl.

[406] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl.

[407] E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[408] In some preferred embodiments, E^5 is C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl.

[409] In some preferred embodiments, E^5 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[410] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^4, or E^5.

[411] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl.

[412] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[413] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_6-alkyl.

[414] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[415] In some preferred embodiments, R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[416] R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

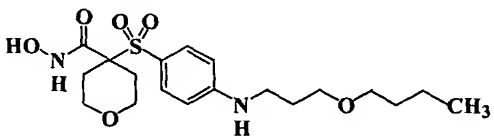
[417] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[418] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

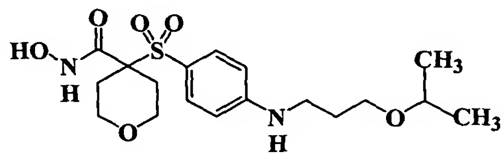
[419] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[420] In some preferred embodiments, E^5 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, or C_1-C_8-alkoxy-C_1-C_8-alkyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN.

[421] In some preferred embodiments, E^5 is C_1-C_8-alkyl. Such compounds include, for example:



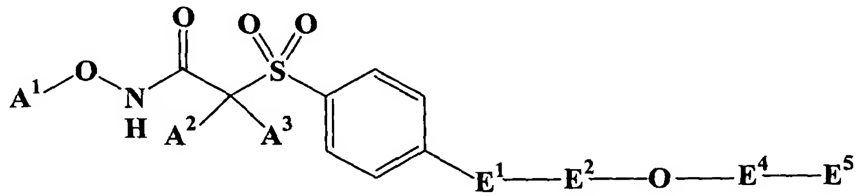
X-1



X-2

Preferred Embodiment No. 10

[422] In some embodiments of this invention, the compound has a structure corresponding to Formula XI:



XI

[423] A^1, A^2, and A^3 are as defined above for Formula I.

[424] E^2 comprises at least 3 carbon atoms. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[425] In some preferred embodiments, E^2 is C_3-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[426] In some preferred embodiments, E^2 is C_3-C_{10}-alkyl optionally is substituted with one or more halogen.

[427] In some preferred embodiments, E^2 is C_3-C_{10}-alkyl.

[428] In some preferred embodiments, E^2 is C_3-C_5-alkyl.

[429] E^5 is -H, alkyl, alkenyl, alkynyl, alkoxyalkyl, carbocyclyl, carbocyclylalkoxyalkyl, heterocyclyl, heterocyclylalkyl, or heterocyclylalkoxyalkyl. The alkyl, alkenyl, alkynyl, and alkoxyalkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The carbocyclyl, carbocyclylalkoxyalkyl, heterocyclyl, heterocyclylalkyl, and heterocyclylalkoxyalkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, halogen-substituted alkoxyalkyl, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl.

[430] In some preferred embodiments, E^5 is -H, C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, carbocyclyl-C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, heterocyclyl, heterocyclyl-C_1-C_{10}-alkyl, or heterocyclyl-C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The carbocyclyl, carbocyclyl-C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, heterocyclyl, heterocyclyl-C_1-C_{10}-alkyl, and heterocyclyl-C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl.

[431] In some preferred embodiments, E^5 is -H, C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The carbocyclyl, carbocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, and

heterocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -N(R^3)(R^4), -C(O)(R^5), -S-R^3, -S(O)$_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[432] R^1 and R^2 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[433] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[434] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[435] R^3 is -H, alkyl, -O-R^4, -N(R^4)(R^5), carbocyclylalkyl, or heterocyclylalkyl. The alkyl, carbocyclylalkyl, or heterocyclylalkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[436] In some preferred embodiments, R^3 is -H, C_1-C_8-alkyl, -O-R^4, -N(R^4)(R^5), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

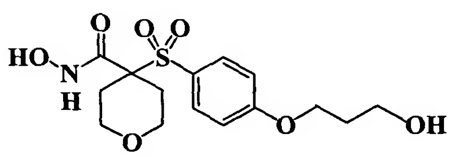
[437] In some preferred embodiments, R^3 is -H, C_1-C_6-alkyl, -O-R^4, -N(R^4)(R^5), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[438] R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

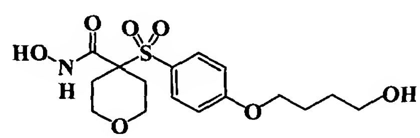
[439] In some preferred embodiments, R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[440] In some preferred embodiments, R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

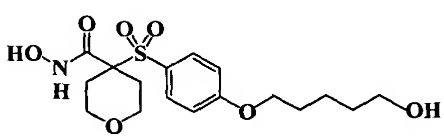
[441] In some preferred embodiments, E^5 is -H, C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, or C_1-C_8-alkoxy-C_1-C_8-alkyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. Such compounds include, for example:



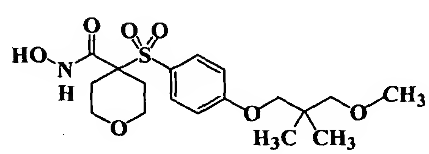
XI-1



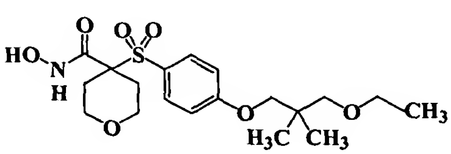
XI-2



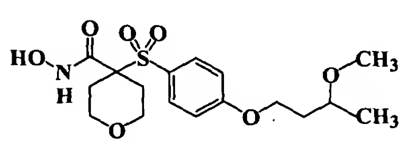
XI-3



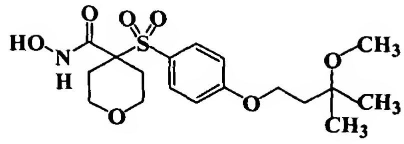
XI-4



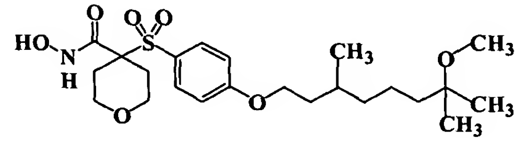
XI-5



XI-6



XI-7

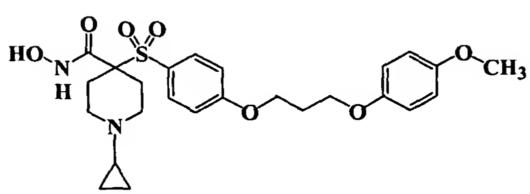


XI-8

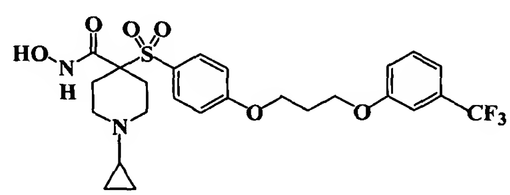
[442] In some preferred embodiments, E^5 is carbocyclyl, carbocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl. the carbocyclyl, carbocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, and heterocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -N(R^3)(R^4), -C(O)(R^5), -S-R^3, -S(O)$_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[443] In some preferred embodiments, E^5 is optionally-substituted carbocyclyl.

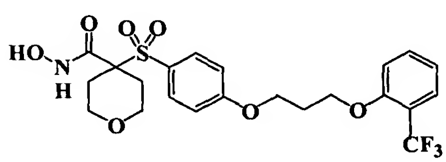
[444] In some preferred embodiments, E^5 is optionally-substituted phenyl. Such compounds include, for example:



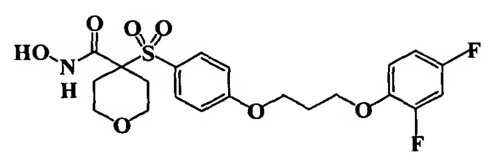
XI-9



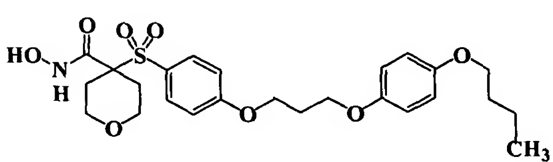
XI-10



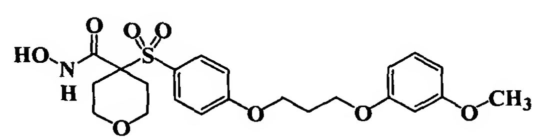
XI-11



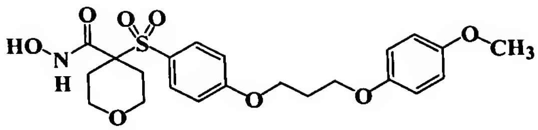
XI-12



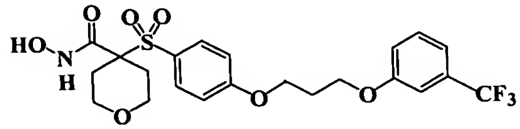
XI-13



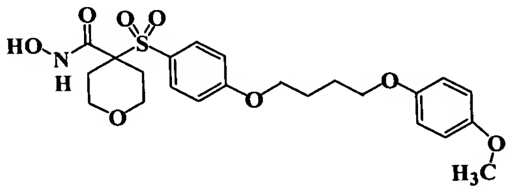
XI-14



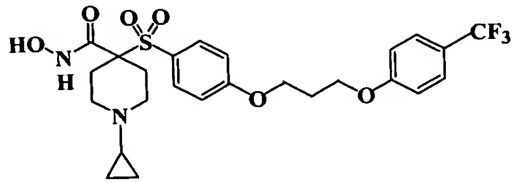
XI-15



XI-16

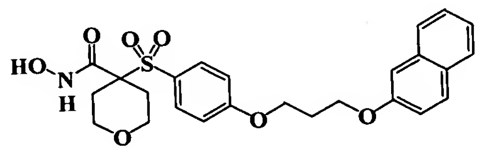


XI-17



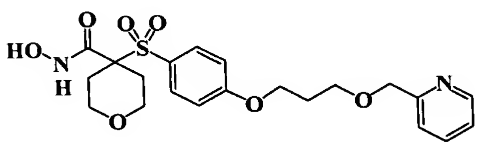
XI-18

[445] In some preferred embodiments, E^5 is optionally-substituted naphthalenyl. Such compounds include, for example:

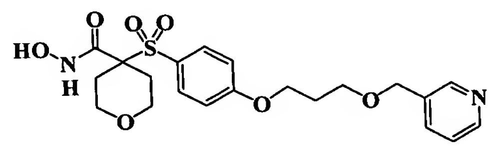


XI-19

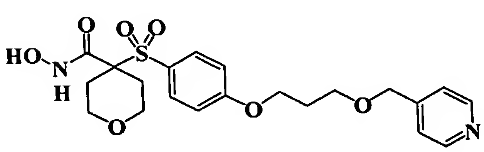
[446] In some preferred embodiments, E^5 is heterocyclyl or heterocyclyl-C_1-C_8-alkyl. Such compounds include, for example:



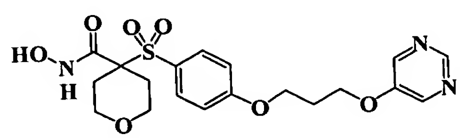
XI-20



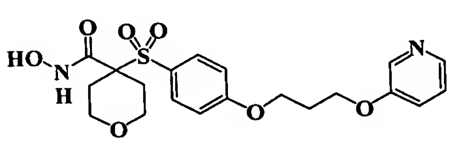
XI-21



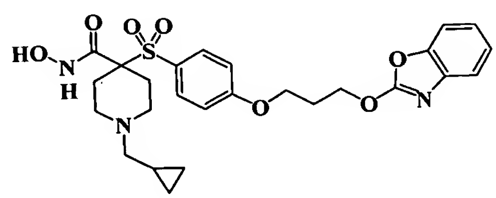
XI-22



XI-23



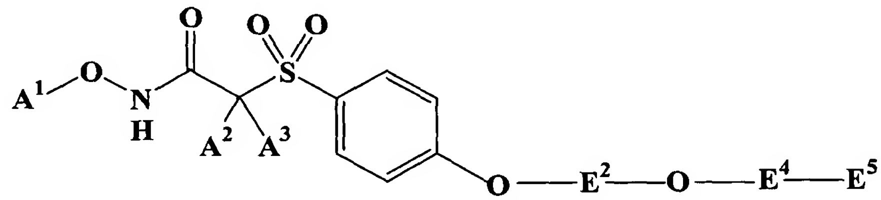
XI-24



XI-24

Preferred Embodiment No. 11

[447] In some embodiments of this invention, the compound has a structure corresponding to Formula XII:



XII

[448] A^1, A^2, and A^3 are as defined above for Formula I.

[449] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted. An atom in E^2 optionally is bound to an atom in E^5 to form a ring.

[450] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents selected from the group consisting of halogen, C_1-C_6-alkyl, halo-C_1-C_6-alkyl.

[451] In some preferred embodiments, E^2 is C_2-C_6-alkyl optionally substituted with one or more halogen.

[452] In some preferred embodiments, E^2 is C_2-C_6-alkyl.

[453] E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

[454] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, or halo-C_2-C_{20}-alkenyl.

[455] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, halo-C_1-C_3-alkyl, C_2-C_3-alkenyl, or halo-C_2-C_3-alkenyl.

[456] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl.

[457] In some preferred embodiments, E^4 is methyl.

[458] In some preferred embodiments, E^4 is a bond.

[459] E^5 is:

an optionally-substituted radical selected from the group consisting of alkenyl, alkynyl, alkoxy, alkoxyalkyl, fused-ring carbocyclyl, and heterocyclyl; or

single-ring carbocyclyl substituted with one or more substituents independently selected from the group consisting of -OH, $-NO_2$, -CN, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, halogen-substituted carbocyclylalkyl, heterocyclyl, haloheterocyclyl, heterocyclylalkyl, and halogen-substituted heterocyclylalkyl; or

single-ring carbocyclyl having multiple substitutions.

[460] In some preferred embodiments, E^5 is C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, heterocyclyl, single-ring carbocyclyl, or fused-ring carbocyclyl. The C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The heterocyclyl and fused-ring carbocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_8-alkyl, and halogen-substituted heterocyclyl-C_1-C_8-alkyl. The single-ring carbocyclyl is either:

substituted with one or more substituents independently selected from the group consisting of -OH, $-NO_2$, -CN, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_8-alkyl, and halogen-substituted heterocyclyl-C_1-C_8-alkyl, or

substituted with 2 or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, halogen-substituted

carbocyclyl-C_1-C_8-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_8-alkyl, and halogen-substituted heterocyclyl-C_1-C_8-alkyl.

[461] In some preferred embodiments, E^5 is C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_2-C_8-alkyl, heterocyclyl, single-ring carbocyclyl, or fused-ring carbocyclyl. The C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The heterocyclyl and fused-ring carbocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -N(R^5)(R^6), -C(O)(R^7), -S-R^5, -S(O)$_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl. The single-ring carbocyclyl is either:

substituted with one or more substituents independently selected from the group consisting of -OH, -NO_2, -CN, -N(R^5)(R^6), -C(O)(R^7), -S-R^5, -S(O)$_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl; or

substituted with 2 or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -N(R^5)(R^6), -C(O)(R^7), -S-R^5, -S(O)$_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl.

[462] R^1 and R^2 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[463] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[464] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[465] R^3 is -H, alkyl, -O-R^4, -N(R^4)(R^5), carbocyclylalkyl, or heterocyclylalkyl. The alkyl, carbocyclylalkyl, or heterocyclylalkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[466] In some preferred embodiments, R^3 is -H, C_1-C_8-alkyl, -O-R^4, -N(R^4)(R^5), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[467] In some preferred embodiments, R^3 is -H, C_1-C_6-alkyl, -O-R^4, -N(R^4)(R^5), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

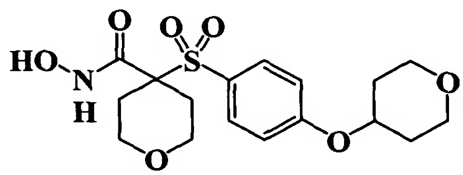
[468] R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[469] In some preferred embodiments, R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[470] In some preferred embodiments, R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl,

heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

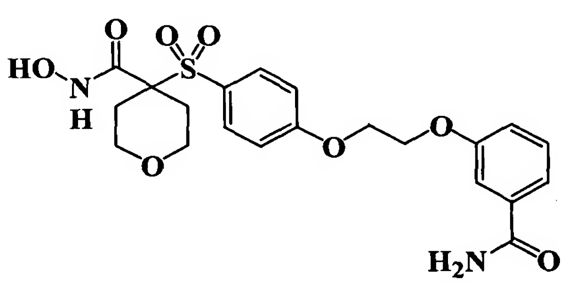
[471] In some preferred embodiments, E^2 is bound to an atom of E^5 to form a ring. Such compounds include, for example:



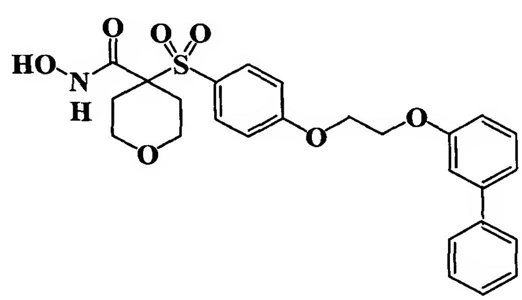
XII-1

[472] In some preferred embodiments, E^2 is not bound to an atom of E^5 to form a ring.

[473] In some such preferred embodiments, E^5 is a single-ring carbocyclyl (preferably phenyl) substituted with one or more substituents independently selected from the group consisting of -OH, $-NO_2$, -CN, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl. Such compounds include, for example:

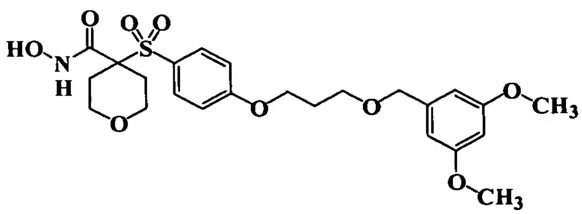


XII-2

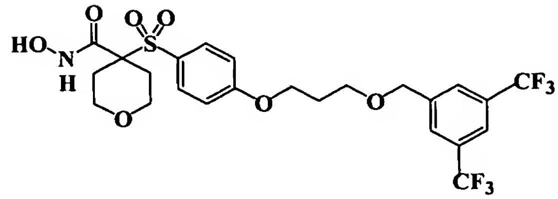


XII-3

[474] In some preferred embodiments, E^5 is single-ring carbocyclyl (preferably phenyl) substituted with 2 or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl. Such compounds include, for example:

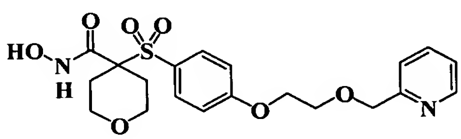


XII-4

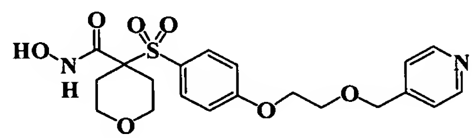


XII-5

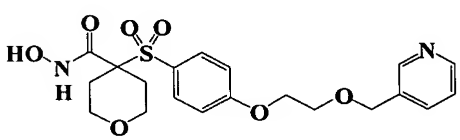
[475] In some preferred embodiments, E^5 is heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl. Such compounds include, for example:



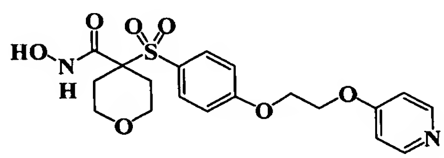
XII-6



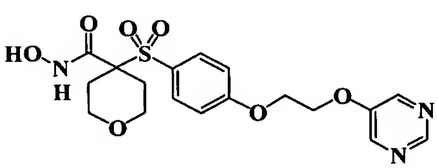
XII-7



XII-8



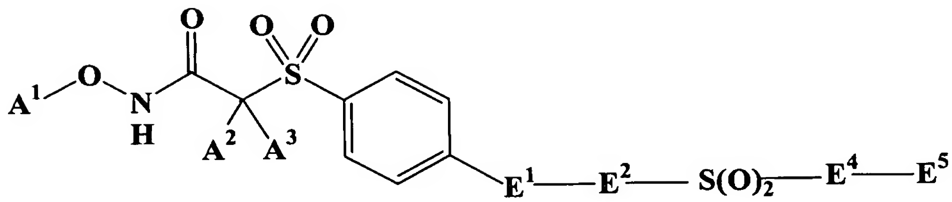
XII-9



XII-10

Preferred Embodiment No. 12

[476] In some embodiments of this invention, the compound has a structure corresponding to Formula XIII:



XIII

[477] A^1, A^2, and A^3 are as defined above for Formula I.

[478] E^1 is -S(O)$_2$-, -S(O)-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-.

[479] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[480] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[481] In some preferred embodiments, E^2 is C_1-C_6-alkyl, cycloalkyl, C_1-C_6-alkylcycloalkyl, cycloalkyl-C_1-C_6-alkyl, or C_1-C_6-alkylcycloalkyl-C_1-C_6-alkyl. Any member of this group optionally is substituted with one or more halogen, although such substituent typically is preferably not substituted with halogen.

[482] E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

[483] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, or halo-C_2-C_{20}-alkenyl.

[484] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, halo-C_1-C_3-alkyl, C_2-C_3-alkenyl, or halo-C_2-C_3-alkenyl.

[485] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl.

[486] E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[487] In some preferred embodiments, E^5 is C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents

independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl.

[488] In some preferred embodiments, E^5 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[489] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^4, or E^5.

[490] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl.

[491] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[492] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_6-alkyl.

[493] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[494] In some preferred embodiments, R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl,

heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[495] R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

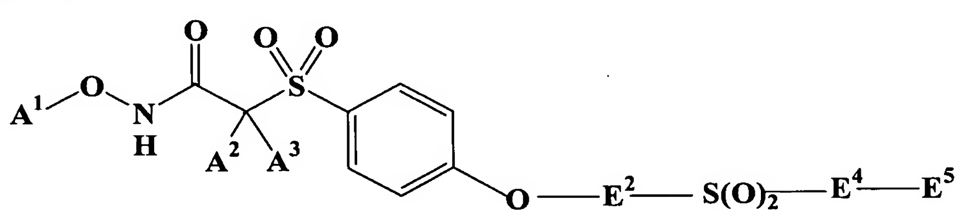
[496] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[497] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[498] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

Preferred Embodiment No. 13

[499] In some embodiments of this invention, the compound has a structure corresponding to Formula XIV:



XIV

[500] A^1, A^2, and A^3 are as defined above for Formula I.

[501] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[502] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[503] In some preferred embodiments, E^2 is C_1-C_6-alkyl optionally substituted with one or more halogen.

[504] In some preferred embodiments, E^2 is C_1-C_6-alkyl.

[505] E^4 is alkyl or alkenyl. The alkyl and alkenyl optionally are substituted.

[506] In some preferred embodiments, E^4 is C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, or halo-C_2-C_{20}-alkenyl.

[507] In some preferred embodiments, E^4 is C_1-C_3-alkyl, halo-C_1-C_3-alkyl, C_2-C_3-alkenyl, or halo-C_2-C_3-alkenyl.

[508] In some preferred embodiments, E^4 is C_1-C_3-alkyl or C_2-C_3-alkenyl.

[509] E^5 is -H, alkyl, alkenyl, alkynyl, alkoxy, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[510] In some preferred embodiments, E^5 is -H, C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, carbocyclyl, or heterocyclyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, and C_1-C_{20}-alkoxy optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl.

[511] In some preferred embodiments, E^5 is -H, C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, carbocyclyl, or heterocyclyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, and C_1-C_8-alkoxy optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more

more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[512] R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[513] In some preferred embodiments, R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

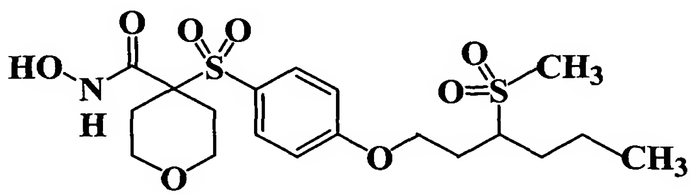
[514] R^5 is -H, C_1-C_8-alkyl, $-O-R^6$, $-N(R^6)(R^7)$, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[515] In some preferred embodiments, R^5 is -H, C_1-C_6-alkyl, $-O-R^6$, $-N(R^6)(R^7)$, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[516] R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[517] In some preferred embodiments, R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

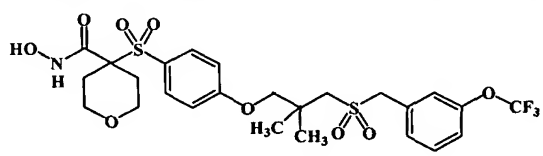
[518] In some preferred embodiments, E^5 is -H, C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, or C_1-C_8-alkoxy. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, and C_1-C_8-alkoxy optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. In one such embodiment, E^5 is C_1-C_8-alkyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. Such compounds include, for example:



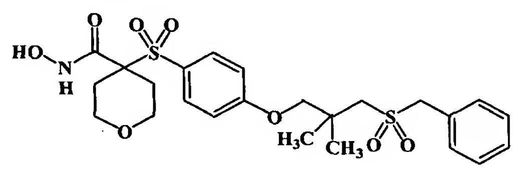
XIV-1

[519] In some preferred embodiments, E^5 is optionally-substituted carbocyclyl and optionally-substituted heterocyclyl.

[520] In some preferred embodiments, E^5 is optionally-substituted aryl, often preferably optionally-substituted phenyl. Such compounds include, for example:



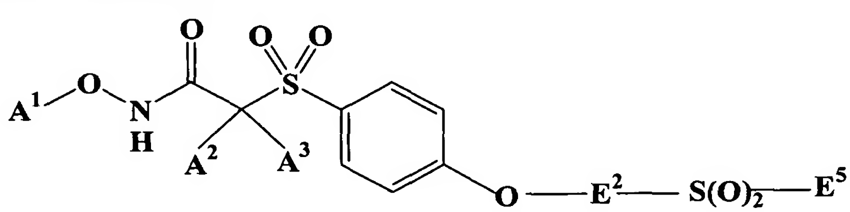
XIV-2



XIV-3

Preferred Embodiment No. 14

[521] In some embodiments of this invention, the compound has a structure corresponding to Formula XV:



XV

[522] A^1, A^2, and A^3 are as defined above for Formula I.

[523] E^2 comprises less than 5 carbon atoms. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted, but preferably is not substituted.

[524] E^5 is alkyl, alkenyl, alkynyl, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[525] In some preferred embodiments, E^5 is C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, -N(R^3)(R^4), -C(O)(R^5), -S-R^3, -S(O)$_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, C_1-C_8-alkylcarbocyclyloxy, and halogen-substituted C_1-C_8-alkylcarbocyclyloxy.

[526] In some preferred embodiments, E^5 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, andC_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -N(R^3)(R^4), -C(O)(R^5), -S-R^3, -S(O)$_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, C_1-C_6-alkylcarbocyclyloxy, and halogen-substituted C_1-C_6-alkylcarbocyclyloxy.

[527] R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[528] In some preferred embodiments, R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[529] R^5 is -H, C_1-C_8-alkyl, -O-R^6, -N(R^6)(R^7), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[530] In some preferred embodiments, R^5 is -H, C_1-C_6-alkyl, -O-R^6, -N(R^6)(R^7), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

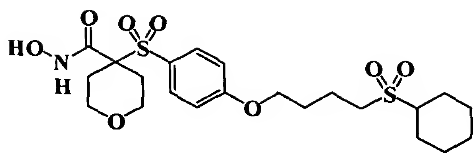
[531] R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[532] In some preferred embodiments, R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

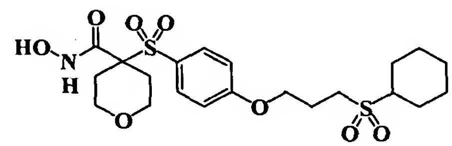
[533] In some preferred embodiments, E^5 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, or C_1-C_8-alkoxy-C_1-C_8-alkyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN.

[534] In some preferred embodiments, E^5 is optionally-substituted carbocyclyl.

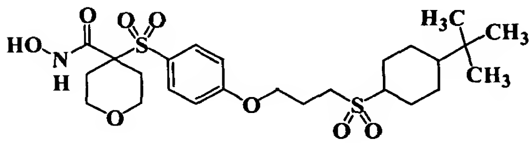
[535] In some preferred embodiments, E^5 is optionally-substituted C_5-C_6-cycloalkyl. Such compounds include, for example:



XV-1

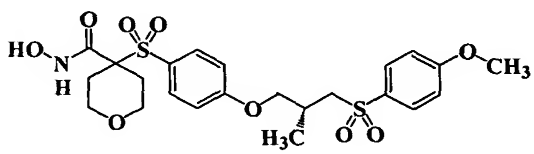


XV-2

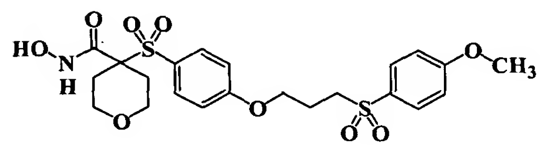


XV-3

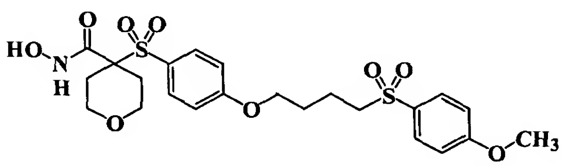
[536] In some preferred embodiments, E^5 is optionally-substituted phenyl. Such compounds include, for example:



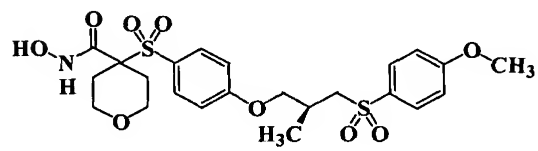
XV-4



XV-5



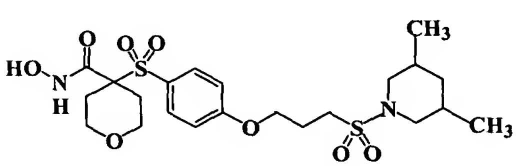
XV-6



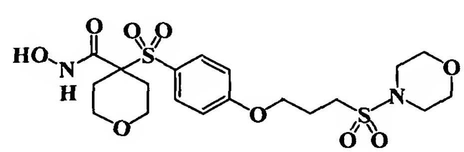
XV-7

[537] In some preferred embodiments, E^5 is optionally-substituted heterocyclyl.

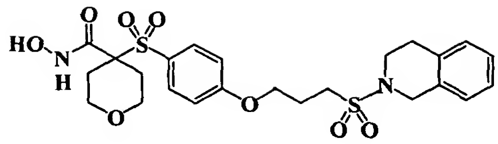
[538] In some preferred embodiments, E^5 is optionally-substituted heterocyclyl selected from the group consisting of piperidinyl, morpholinyl, and tetrahydroisoquinolinyl . Such compounds include, for example:



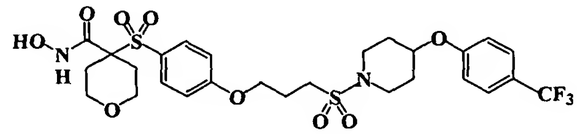
XV-8



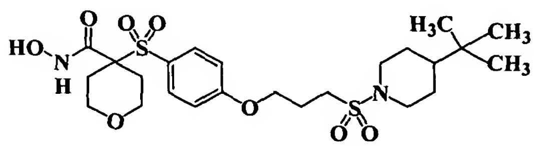
XV-9



XV-10



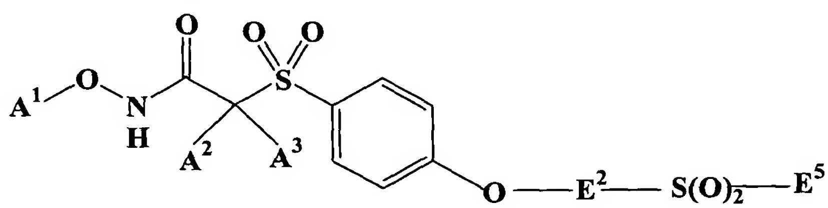
XV-11



XV-12

Preferred Embodiment No. 15

[539] In some embodiments of this invention, the compound has a structure corresponding to Formula XVI:



XVI

[540] A^1, A^2, and A^3 are as defined above for Formula I.

[541] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[542] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, halo-C_1-C_6-alkyl.

[543] In some preferred embodiments, E^2 is C_1-C_6-alkyl optionally substituted with one or more halogen.

[544] In some preferred embodiments, E^2 is C_1-C_6-alkyl.

[545] E^5 is alkyl, alkenyl, alkynyl, alkoxyalkyl, saturated carbocyclyl, partially saturated carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[546] In some preferred embodiments, E^5 is C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, saturated carbocyclyl, partially saturated carbocyclyl, or heterocyclyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The saturated carbocyclyl, partially saturated carbocyclyl, and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, -N(R^3)(R^4), -C(O)(R^5), -S-R^3, -S(O)$_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, C_1-C_8-alkylcarbocyclyloxy, and halogen-substituted C_1-C_8-alkylcarbocyclyloxy.

[547] In some preferred embodiments, E^5 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, saturated carbocyclyl, partially saturated carbocyclyl, or heterocyclyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The saturated carbocyclyl, partially saturated carbocyclyl, and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -N(R^3)(R^4), -C(O)(R^5), -S-R^3, -S(O)$_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, C_1-C_6-alkylcarbocyclyloxy, and halogen-substituted C_1-C_6-alkylcarbocyclyloxy.

[548] R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[549] In some preferred embodiments, R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[550] R^5 is s -H, C_1-C_8-alkyl, -O-R^6, -N(R^6)(R^7), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[551] In some preferred embodiments, R^5 is -H, C_1-C_6-alkyl, -O-R^6, -N(R^6)(R^7), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

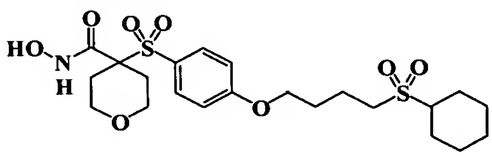
[552] R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[553] In some preferred embodiments, R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

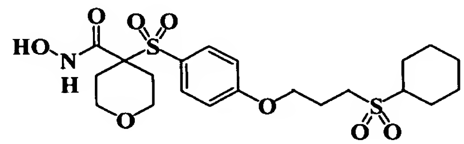
[554] In some preferred embodiments, E^5 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, or C_1-C_8-alkoxy-C_1-C_8-alkyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN.

[555] In some preferred embodiments, E^5 is optionally-substituted, partially-saturated carbocyclyl.

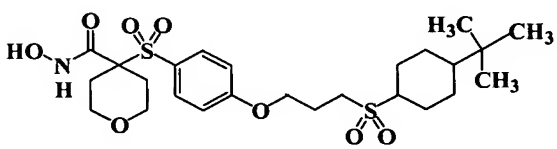
[556] In some preferred embodiments, E^5 is optionally-substituted, saturated carbocyclyl (preferably optionally-substituted C_5-C_6 cycloalkyl). Such compounds include, for example:



XVI-1

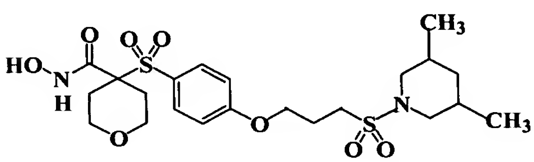


XVI-2

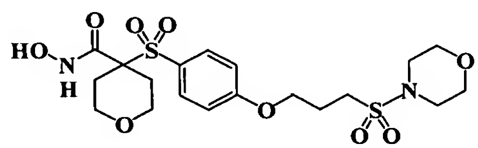


XVI-3

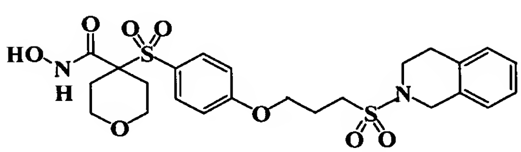
[557] In some preferred embodiments, E^5 is optionally-substituted heterocyclyl. Such compounds include, for example:



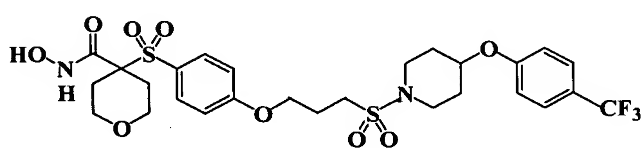
XVI-4



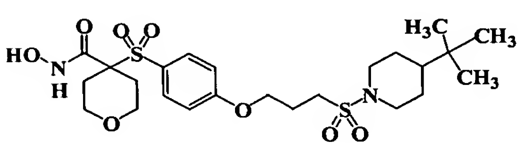
XVI-5



XVI-6



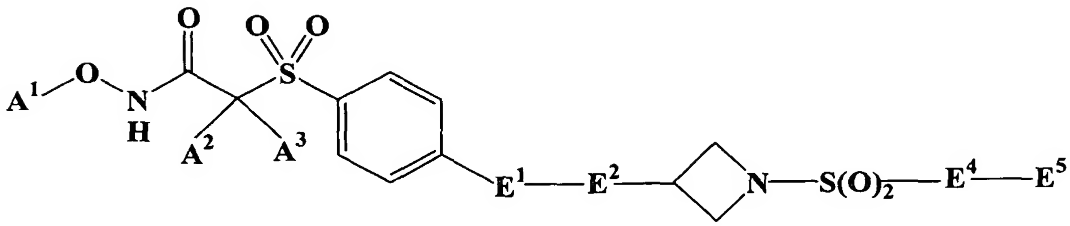
XVI-7



XVI-8

Preferred Embodiment No. 16

[558] In some embodiments of this invention, the compound has a structure corresponding to Formula XVII:



XVII

[559] A^1, A^2, and A^3 are as defined above for Formula I.

[560] E^1 is $-S(O)_2-$, $-S(O)-$, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

[561] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[562] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[563] In some preferred embodiments, E^2 is C_1-C_6-alkyl optionally substituted with one or more halogen.

[564] In some preferred embodiments, E^2 is C_1-C_6-alkyl.

[565] E^4 is a bond, alkyl, or alkenyl, The alkyl and alkenyl optionally are substituted.

[566] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, or halo-C_2-C_{20}-alkenyl.

[567] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, halo-C_1-C_3-alkyl, C_2-C_3-alkenyl, or halo-C_2-C_3-alkenyl.

[568] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl.

[569] E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[570] In some preferred embodiments, E^5 is C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The

carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl.

[571] In some preferred embodiments, E^5 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[572] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^4, or E^5.

[573] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl.

[574] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[575] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_6-alkyl.

[576] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[577] In some preferred embodiments, R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[578] R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

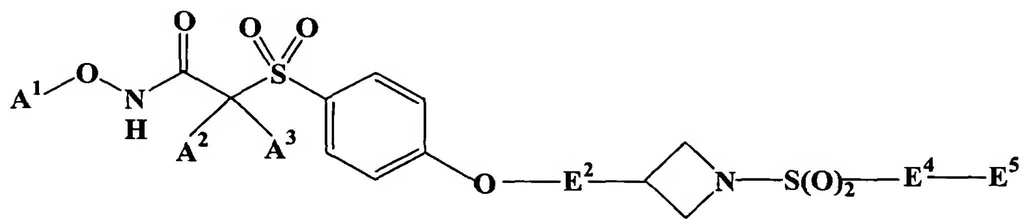
[579] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[580] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[581] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

Preferred Embodiment No. 17

[582] In some embodiments of this invention, the compound has a structure corresponding to Formula XVII:



XVIII

[583] A^1, A^2, and A^3 are as defined above for Formula I.

[584] E^2 is a bond, alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[585] In some preferred embodiments, E^2 is a bond, C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[586] In some preferred embodiments, E^2 is a bond, C_1-C_6-alkyl, or halo-C_1-C_6-alkyl.

[587] In some preferred embodiments, E^2 is a bond or C_1-C_6-alkyl.

[588] In some preferred embodiments, E^2 is a bond.

[589] E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

[590] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, or halo-C_2-C_{20}-alkenyl.

[591] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, halo-C_1-C_3-alkyl, C_2-C_3-alkenyl, or halo-C_2-C_3-alkenyl.

[592] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl.

[593] In some preferred embodiments, E^4 is a bond.

[594] E^5 is optionally-substituted heterocyclyl or substituted carbocyclyl.

[595] The E^5 heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, halogen-substituted alkoxyalkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl.

[596] In some preferred embodiments, E^5 is heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_6-alkyl, -N(R^3)(R^4), -C(O)(R^5), -S-R^3, -S(O)$_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl.

[597] In some preferred embodiments, E^5 is heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -N(R^3)(R^4), -C(O)(R^5), -S-R^3, -S(O)$_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[598] The E^5 carbocyclyl is substituted with:

2 or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, halogen-substituted alkoxyalkyl, -N(R^3)(R^4), -C(O)(R^5), -S-R^3, -S(O)$_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl; or

a substituent selected from the group consisting of halogen, -OH, -NO_2, -CN, -C(O)-O-R^3, -S-R^3, -S(O)$_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl.

[599] In some preferred embodiments, E^5 is carbocyclyl substituted with:

2 or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, -N(R^3)(R^4), -C(O)(R^5), -S-R^3, -S(O)$_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl, or

a substituent selected from the group consisting of halogen, -OH, $-NO_2$, -CN, -C(O)-O-R^3, -S-R^3, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl.

[600] In some preferred embodiments, E^5 is carbocyclyl substituted with:

2 or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -N(R^3)(R^4), -C(O)(R^5), -S-R^3, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl, or

a substituent selected from the group consisting of halogen, -OH, $-NO_2$, -CN, -C(O)-O-R^3, -S-R^3, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[601] R^3 and R^4 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[602] In some preferred embodiments, R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[603] In some preferred embodiments, R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[604] R^5 is -H, alkyl, -O-R^6, -N(R^6)(R^7), carbocyclylalkyl, or heterocyclylalkyl. The alkyl, carbocyclylalkyl, or heterocyclylalkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[605] In some preferred embodiments, R^5 is -H, C_1-C_8-alkyl, -O-R^6, -N(R^6)(R^7), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl,

carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[606] In some preferred embodiments, R^5 is -H, C_1-C_6-alkyl, -O-R^6, -N(R^6)(R^7), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

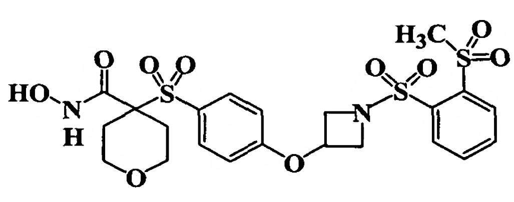
[607] R^6 and R^7 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[608] In some preferred embodiments, R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

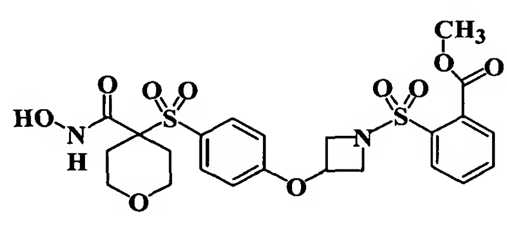
[609] In some preferred embodiments, R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[610] In some preferred embodiments, E^5 is optionally-substituted heterocyclyl.

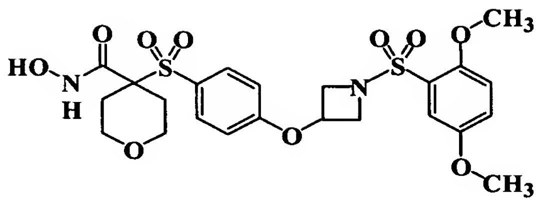
[611] In some preferred embodiments, E^5 is substituted carbocyclyl (preferably substituted phenyl). Such compounds include, for example:



XVIII-1



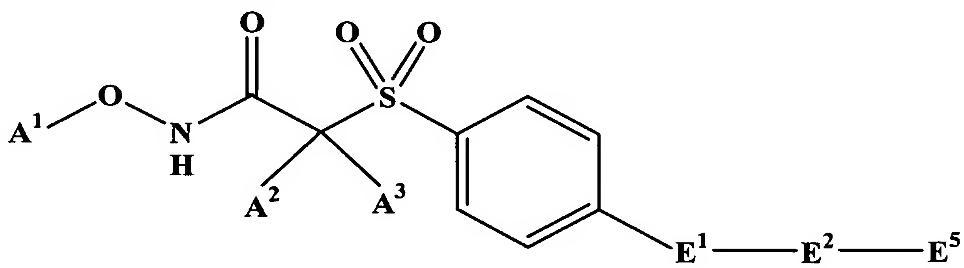
XVIII-2



XVIII-3

Preferred Embodiment No. 18

[612] In some embodiments of this invention, the compound has a structure corresponding to Formula XVIII:



XIX

[613] A^1, A^2 and A^3 are as defined above for Formula I.

[614] E^1 is -O-, -S(O)$_2$-, -S(O)-, -S-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-.

[615] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[616] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkyl-cycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkyl-cycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more halogen.

[617] In some preferred embodiments, E^2 is C_1-C_6-alkyl. The alkyl optionally is substituted with one or more halogen.

[618] E^5 is substituted heterocyclyl.

[619] In some preferred embodiments, E^5 is heterocyclyl that is:

substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl,

$-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, and carbocyclyl-C_1-C_6-alkyl, and/or

substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_5-C_6-cycloalkyl or halo-C_5-C_6-cycloalkyl.

[620] In some preferred embodiments, E^5 is heterocyclyl that is:

substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl, and/or

substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_5-C_6-cycloalkyl or halo-C_5-C_6-cycloalkyl.

[621] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted.

[622] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl.

[623] R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl.

[624] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

[625] In some preferred embodiments, R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

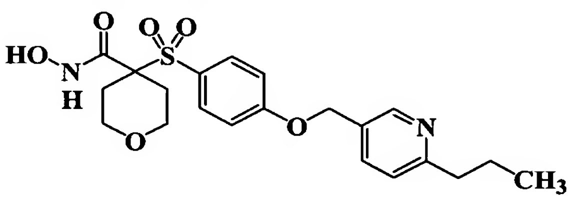
[626] R^7 is -H, C_1-C_8-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The alkyl, carbocyclylalkyl, or heterocyclylalkyl may be substituted with one or more halogen.

[627] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The alkyl, carbocyclylalkyl, and heterocyclylalkyl optionally are substituted with one or more halogen.

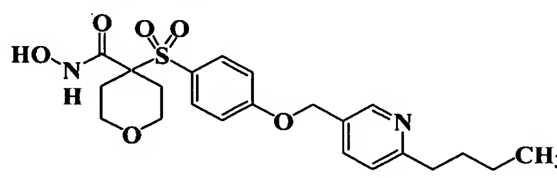
[628] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

[629] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is –H, any member of this group optionally is substituted with one or more halogen.

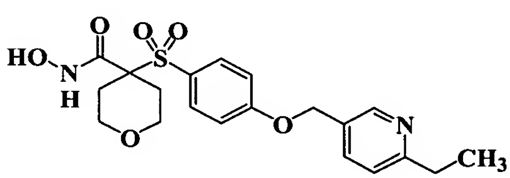
[630] Compounds of this embodiment include, for example:



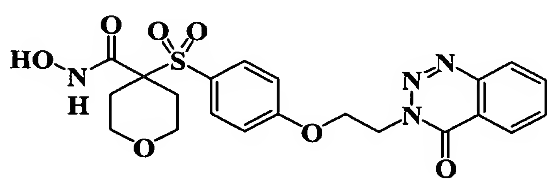
XIX-1



XIX-2



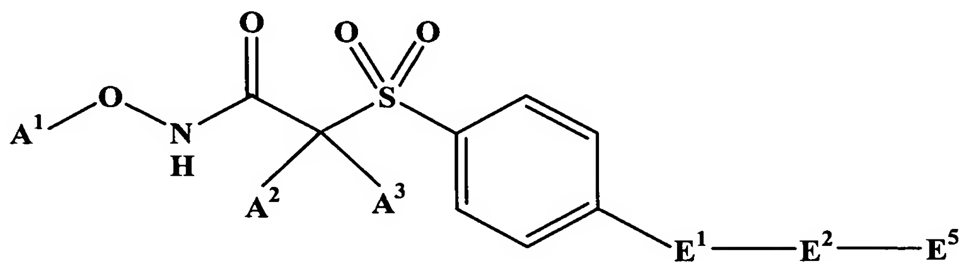
XIX -3



XIX -4

Preferred Embodiment No. 19

[631] In some embodiments of this invention, the compound has a structure corresponding to Formula XIX:



XX

[632] A^1, A^2, and A^3 are as defined above for Formula I.

[633] E^1 is -O-, -S(O)$_2$-, -S(O)-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-.

[634] E^2 comprises at least two carbon atoms. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[635] In some preferred embodiments, E^2 is C_2-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkyl-cycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkyl-cycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more halogen.

[636] In some preferred embodiments, E^2 is C_2-C_6-alkyl. The alkyl may optionally be substituted with one or more halogen.

[637] E^5 is optionally-substituted heterocyclyl.

[638] In some preferred embodiments, E^5 is heterocyclyl that is:

optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO$_2$, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, -N(R^5)(R^6), -C(O)(R^7), -S-R^5, -S(O)$_2$-R^5, carbocyclyl, halocarbocyclyl, and carbocyclyl-C_1-C_6-alkyl, and/or

optionally substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_5-C_6-cycloalkyl or halo-C_5-C_6-cycloalkyl.

[639] In some preferred embodiments, E^5 is heterocyclyl that is:

optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO$_2$, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl,

halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -N(R^5)(R^6), -C(O)(R^7), -S-R^5, -S(O)$_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl, and

optionally substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_5-C_6-cycloalkyl or halo-C_5-C_6-cycloalkyl.

[640] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted.

[641] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl.

[642] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[643] R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl.

[644] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is –H, any member of this group optionally is substituted with one or more halogen.

[645] In some preferred embodiments, R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is –H, any member of this group optionally is substituted with one or more halogen.

[646] R^7 is -H, C_1-C_8-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The alkyl, carbocyclylalkyl, and heterocyclylalkyl optionally are substituted with one or more halogen.

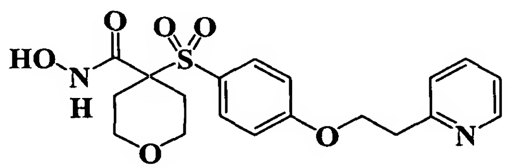
[647] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The alkyl, carbocyclylalkyl, and heterocyclylalkyl optionally are substituted with one or more halogen.

[648] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and

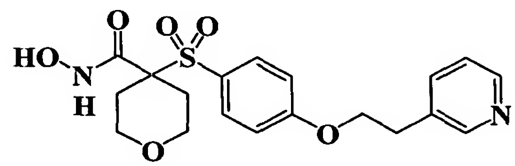
heterocyclyl-C_1-C_8-alkyl. Except where the member is –H, any member of this group optionally is substituted with one or more halogen.

[649] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is –H, any member of this group optionally is substituted with one or more halogen.

[650] Some particularly preferred compounds include:



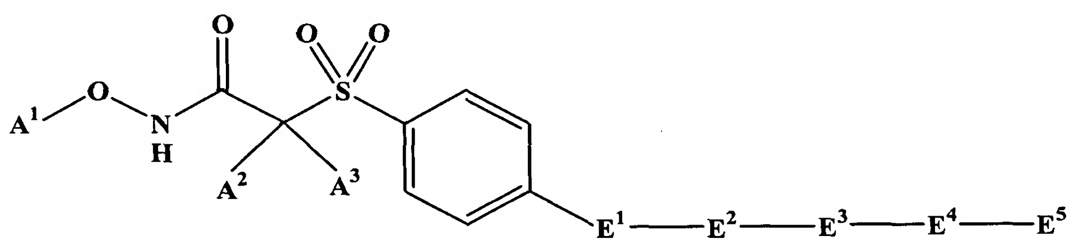
XX-1



XX-2

Preferred Embodiment No. 20

[651] In some embodiments of this invention, the compound has a structure corresponding to Formula XX:



XXI

[652] A^1, A^2, and A^3 are as defined above for Formula I.

[653] E^1 is -O-, -S(O)$_2$-, -S(O)-, -S-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-.

[654] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[655] In some preferred embodiments, E^2 is C_2-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[656] In some preferred embodiments, E^2 is C_2-C_6-alkyl. The alkyl may optionally be substituted with one or more halogen.

[657] E^3 is -C(O)-, -O-(CO)-, -C(O)-O-, -C(NR^3)-, -N(R^4)-, -N(R^4)-C(NR^3)-, -C(NR^3)-N(R^4)-, -C(O)-N(R^4)-, -N(R^4)-C(O)-, -N(R^4)-C(O)-N(R^5)-, -S-, -S(O)-, -N(R^4)-$S(O)_2$-, -$S(O)_2$-N(R^4)-, -C(O)-N(R^4)-N(R^5)-C(O)-, -C(R^4)(R^6)-C(O)-, or -C(R^7)(R^8)-.

[658] E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

[659] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, or C_2-C_{20}-alkenyl. The alkyl and alkenyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, and carbocyclyl. The carbocyclyl, in turn, optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl.

[660] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl. The alkyl and alkenyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen and carbocyclyl. The carbocyclyl, in turn, optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[661] E^5 is carbocyclyl or heterocyclyl. The carbocyclyl and heterocyclyl are:

substituted with a substituent selected from the group consisting of optionally-substituted carbocyclyl, optionally-substituted carbocyclylalkyl, optionally-substituted heterocyclyl, and optionally-substituted heterocyclylalkyl, and

optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, alkyl, alkoxy, alkoxyalkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, carbocyclyl, carbocyclylalkyl, haloalkyl, haloalkoxy, halogen-substituted alkoxyalkyl, halocarbocyclyl, halogen-substituted carbocyclylalkyl, hydroxycarbocyclyl, and heteroaryl.

[662] In some preferred embodiments, E^5 is carbocyclyl or heterocyclyl. The carbocyclyl and heterocyclyl are:

substituted with a substituent selected from the group consisting of optionally-substituted carbocyclyl, optionally-substituted carbocyclyl-C_1-C_8-alkyl, optionally-substituted heterocyclyl, and optionally-substituted heterocyclyl-C_1-C_8-alkyl, and

optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, halocarbocyclyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, hydroxycarbocyclyl, and heteroaryl.

[663] In some preferred embodiments, E^5 is carbocyclyl or heterocyclyl, wherein the carbocyclyl and heterocyclyl are:

substituted with a substituent selected from the group consisting of optionally-substituted carbocyclyl, optionally-substituted carbocyclyl-C_1-C_6-alkyl, optionally-substituted heterocyclyl, and optionally-substituted heterocyclyl-C_1-C_6-alkyl, and

optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halocarbocyclyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, hydroxycarbocyclyl, and heteroaryl.

[664] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted.

[665] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl.

[666] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[667] R^3 is -H or -OH.

[668] R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group optionally is substituted.

[669] In some preferred embodiments, R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is –H, any member of this group optionally is substituted with one or more halogen.

[670] In some preferred embodiments, R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

[671] R^6 is -CN or –OH.

[672] R^7 is -H, halogen, -OH, alkyl, alkoxy, or alkoxyalkyl. The alkyl, alkoxy, and alkoxyalkyl optionally are substituted.

[673] In some preferred embodiments, R^7 is -H, halogen, -OH, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, or halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl.

[674] In some preferred embodiments, R^7 is -H, halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, or halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl.

[675] R^8 is -OH or alkoxy. The alkoxy optionally is substituted.

[676] In some preferred embodiments, R^8 is -OH, C_1-C_8-alkoxy, or halo-C_1-C_8-alkoxy.

[677] In some preferred embodiments, R^8 is -OH, C_1-C_6-alkoxy, or halo-C_1-C_6-alkoxy.

[678] R^9 and R^{10} are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl.

[679] R^{11} and R^{12} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is –H, any member of this group optionally is substituted with one or more halogen.

[680] In some preferred embodiments, R^{11} and R^{12} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

[681] In some preferred embodiments, R^{11} and R^{12} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

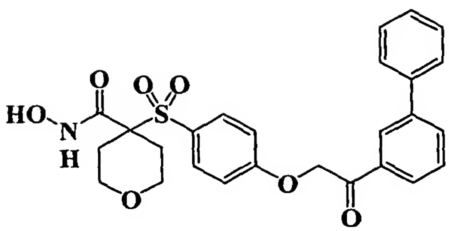
[682] R^{13} is -H, C_1-C_8-alkyl, -O-R^{14}, -N(R^{14})(R^{15}), carbocyclyl-C_1-C_8-alkyl, heterocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, or halogen-substituted heterocyclyl-C_1-C_8-alkyl.

[683] In some preferred embodiments, R^{13} is of -H, C_1-C_6-alkyl, -O-R^{14}, -N(R^{14})(R^{15}), carbocyclyl-C_1-C_6-alkyl, heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, or halogen-substituted heterocyclyl-C_1-C_6-alkyl.

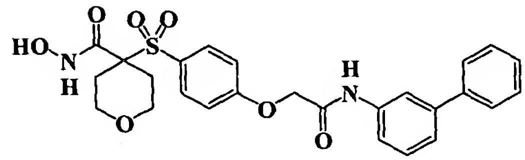
[684] R^{14} and R^{15} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is –H, any member of this group optionally is substituted with one or more halogen.

[685] In some preferred embodiments, R^{14} and R^{15} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

Some preferred compounds include, for example:



XXI-1



XXI-2

A-2. Preferred Selectivities

[686] The hydroxamate compound or salt preferably has an inhibitory activity against MMP-1 or MMP-14 that is substantially less than its inhibitory activity against MMP-2, MMP-9, or MMP-13. In other words, the hydroxamate compound or salt preferably has an in inhibition constant (K_i) against at least one of MMP-2, MMP-9, and MMP-13 that is no greater than about 0.1 times its inhibition constant(s) against at least one of MMP-1 and MMP-14. The inhibition constant of a compound or salt thereof may be determined using an *in vitro* inhibition assay, such as the K_i assay described below in Examples 55-89.

[687] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has a K_i against MMP-2 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14.

[688] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has a K_i against MMP-9 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14.

[689] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has a K_i against MMP-13 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14. It is believed

that such a selectivity profile is often particularly preferred when preventing or treating, for example, a cardiovascular condition or arthritis.

[690] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has K_i's against both MMP-2 and MMP-9 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, or an ophthalmologic condition.

[691] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has K_i's against all of MMP-2, MMP-9, and MMP-13 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, arthritis, or an ophthalmologic condition.

[692] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has a K_i against MMP-2 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both MMP-1 and MMP-14.

[693] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has a K_i against MMP-9 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both MMP-1 and MMP-14.

[694] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has a K_i against MMP-13 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both MMP-1 and MMP-14. It is believed that such a

selectivity profile is often particularly preferred when preventing or treating, for example, a cardiovascular condition or arthritis.

[695] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has K_i's against both MMP-2 and MMP-9 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, or an ophthalmologic condition.

[696] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has K_i's against all of MMP-2, MMP-9, and MMP-3 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, arthritis, or an ophthalmologic condition.

[697] The activity and selectivity of a hydroxamate compound or salt may alternatively be determined using an *in vitro* IC_{50} assay, such as the IC_{50} assay described below in Examples 55-89. In that instance, the hydroxamate compound or salt preferably has an IC_{50} value against at least one of MMP-2, MMP-9, and MMP-13 that is no greater than about 0.1 times its IC_{50} value(s) against at least one of MMP-1 and MMP-14.

[698] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has an IC_{50} value against MMP-2 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14.

[699] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has an IC_{50} value against MMP-9 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no

greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14.

[700] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has an IC_{50} value against MMP-13 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, a cardiovascular condition or arthritis.

[701] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has IC_{50} values against both MMP-2 and MMP-9 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, or an ophthalmologic condition.

[702] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has IC_{50} values against all of MMP-2, MMP-9, and MMP-13 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, arthritis, or an ophthalmologic condition.

[703] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has an IC_{50} value against MMP-2 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both MMP-1 and MMP-14.

[704] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has an IC_{50} value against MMP-9 that is no greater than about 0.1 (more

preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both MMP-1 and MMP-14.

[705] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has an IC_{50} value against MMP-13 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, a cardiovascular condition or arthritis.

[706] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has IC_{50} values against both MMP-2 and MMP-9 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, or an ophthalmologic condition.

[707] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has IC_{50} values against all of MMP-2, MMP-9, and MMP-3 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, arthritis, or an ophthalmologic condition.

B. Salts of the Compounds of this Invention

[708] The compounds of this invention can be used in the form of salts derived from inorganic or organic acids. Depending on the particular compound, a salt of the compound may be advantageous due to one or more of the salt's physical properties, such as enhanced pharmaceutical stability in differing temperatures and humidities, or a

desirable solubility in water or oil. In some instances, a salt of a compound also may be used as an aid in the isolation, purification, and/or resolution of the compound.

[709] Where a salt is intended to be administered to a patient (as opposed to, for example, being used in an *in vitro* context), the salt preferably is pharmaceutically acceptable. Pharmaceutically acceptable salts include salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. In general, these salts typically may be prepared by conventional means with a compound of this invention by reacting, for example, the appropriate acid or base with the compound.

[710] Pharmaceutically-acceptable acid addition salts of the compounds of this invention may be prepared from an inorganic or organic acid. Examples of suitable inorganic acids include hydrochloric, hydrobromic acid, hydroionic, nitric, carbonic, sulfuric, and phosphoric acid. Suitable organic acids generally include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclyl, carboxylic, and sulfonic classes of organic acids. Specific examples of suitable organic acids include acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, toluenesulfonate, 2-hydroxyethanesulfonate, sufanilate, cyclohexylaminosulfonate, algenic acid, b-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, bisulfate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and undecanoate.

[711] Pharmaceutically-acceptable base addition salts of the compounds of this invention include, for example, metallic salts and organic salts. Preferred metallic salts include alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts, and other physiological acceptable metal salts. Such salts may be made from aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc. Preferred organic salts can be made from tertiary amines and quaternary amine salts, such as tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen-containing groups can be

quaternized with agents such as lower alkyl (C_1-C_6) halides *(e.g.,* methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates *(e.g.,* dimethyl, diethyl, dibuytl, and diamyl sulfates), long chain halides *(e.g.,* decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), aralkyl halides *(e.g.,* benzyl and phenethyl bromides), and others.

[712] Particularly preferred salts of the compounds of this invention include hydrochloric acid (HCl) salts and trifluoroacetate (CF_3COOH or TFA) salts.

C. Preventing or Treating Conditions Using the Compounds and Salts of this Invention

[713] One embodiment of this invention is directed to a process for preventing or treating a pathological condition associated with MMP activity in a mammal *(e.g.,* a human, companion animal, farm animal, laboratory animal, zoo animal, or wild animal) having or disposed to having such a condition. Such a condition may be, for example, tissue destruction, a fibrotic disease, pathological matrix weakening, defective injury repair, a cardiovascular disease, a pulmonary disease, a kidney disease, a liver disease, an ophthalmologic disease, or a central nervous system disease. Specific examples of such conditions include osteoarthritis, rheumatoid arthritis, septic arthritis, tumor invasion, tumor metastasis, tumor angiogenesis, a decubitis ulcer, a gastric ulcer, a corneal ulcer, periodontal disease, liver cirrhosis, fibrotic lung disease, otosclerosis, atherosclerosis, multiple sclerosis, dilated cardiomyopathy, epidermal ulceration, epidermolysis bullosa, aortic aneurysm, weak injury repair, an adhesion, scarring, congestive heart failure, post myocardial infarction, coronary thrombosis, emphysema, proteinuria, bone disease, chronic obstructive pulmonary diseases, and Alzheimer's disease.

[714] In some particularly preferred embodiments, the condition comprises arthritis.

[715] In some particularly preferred embodiments, the condition comprises tumor invasion, tumor metastasis, or tumor angiogenesis.

[716] In some particularly preferred embodiments, the condition comprises periodontal disease.

[717] In some particularly preferred embodiments, the condition comprises atherosclerosis.

[718] In some particularly preferred embodiments, the condition comprises multiple sclerosis.

[719] In some particularly preferred embodiments, the condition comprises dilated cardiomyopathy.

[720] In some particularly preferred embodiments, the condition comprises post myocardial infarction.

[721] In some particularly preferred embodiments, the condition comprises congestive heart failure.

[722] In some particularly preferred embodiments, the condition comprises chronic obstructive pulmonary disease.

[723] The condition may alternatively (or additionally) be associated with TNF-α convertase activity. Examples of such a condition include inflammation (*e.g.*, rheumatoid arthritis), autoimmune disease, graft rejection, multiple sclerosis, a fibrotic disease, cancer, an infectious disease (*e.g.*, malaria, mycobacterial infection, meningitis, etc.), fever, psoriasis, a cardiovascular disease (*e.g.*, post-ischemic reperfusion injury and congestive heart failure), a pulmonary disease, hemorrhage, coagulation, hyperoxic alveolar injury, radiation damage, acute phase responses like those seen with infections and sepsis and during shock (*e.g.*, septic shock, hemodynamic shock, etc.), cachexia, and anorexia.

[724] The condition may alternatively (or additionally) be associated with aggrecanase activity. Examples of such a condition include inflammation diseases (*e.g.*, osteoarthritis, rheumatoid arthritis, joint injury, reactive arthritis, acute pyrophosphate arthritis, and psoriatic arthritis) and cancer.

[725] In this patent, the phrase "preventing a condition" means reducing the risk of (or delaying) the onset of the condition in a mammal that does not have the condition, but is predisposed to having the condition. In contrast, the phrase "treating a condition" means ameliorating, suppressing, or eradicating an existing condition. The pathological condition may be (a) the result of pathological MMP activity itself, and/or (b) affected by MMP activity (*e.g.*, diseases associated with TNF-α).

[726] A wide variety of methods may be used alone or in combination to administer the hydroxamates and salt thereof described above. For example, the

hydroxamates or salts thereof may be administered orally, parenterally, by inhalation spray, rectally, or topically.

[727] Typically, a compound (or pharmaceutically acceptable salt thereof) described in this patent is administered in an amount effective to inhibit a target MMP(s). The target MMP is/are typically MMP-2, MMP-9, and/or MMP-13, with MMP-13 often being a particularly preferred target. The preferred total daily dose of the hydroxamate or salt thereof (administered in single or divided doses) is typically from about 0.001 to about 100 mg/kg, more preferably from about 0.001 to about 30 mg/kg, and even more preferably from about 0.01 to about 10 mg/kg (*i.e.*, mg hydroxamate or salt thereof per kg body weight). Dosage unit compositions can contain such amounts or submultiples thereof to make up the daily dose. In many instances, the administration of the compound or salt will be repeated a plurality of times. Multiple doses per day typically may be used to increase the total daily dose, if desired.

[728] Factors affecting the preferred dosage regimen include the type, age, weight, sex, diet, and condition of the patient; the severity of the pathological condition; the route of administration; pharmacological considerations, such as the activity, efficacy, pharmacokinetic, and toxicology profiles of the particular hydroxamate or salt thereof employed; whether a drug delivery system is utilized; and whether the hydroxamate or salt thereof is administered as part of a drug combination. Thus, the dosage regimen actually employed can vary widely, and, therefore, can deviate from the preferred dosage regimen set forth above.

D. Pharmaceutical Compositions Containing the Compounds and Salts of this Invention

[729] This invention also is directed to pharmaceutical compositions comprising a hydroxamate or salt thereof described above, and to methods for making pharmaceutical compositions (or medicaments) comprising a hydroxamate or salt thereof described above.

[730] The preferred composition depends on the method of administration, and typically comprises one or more conventional pharmaceutically acceptable carriers, adjuvants, and/or vehicles. Formulation of drugs is generally discussed in, for example, Hoover, John E., *Remington's Pharmaceutical Sciences* (Mack Publishing Co., Easton, PA: 1975). See also, Liberman, H.A. *See also*, Lachman, L., eds., *Pharmaceutical Dosage Forms* (Marcel Decker, New York, N.Y., 1980).

[731] Solid dosage forms for oral administration include, for example, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the hydroxamates or salts thereof are ordinarily combined with one or more adjuvants. If administered *per os*, the hydroxamates or salts thereof can be mixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation, as can be provided in a dispersion of the hydroxamate or salt thereof in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms also can comprise buffering agents, such as sodium citrate, or magnesium or calcium carbonate or bicarbonate. Tablets and pills additionally can be prepared with enteric coatings.

[732] Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (*e.g.*, water). Such compositions also can comprise adjuvants, such as wetting, emulsifying, suspending, flavoring (*e.g.*, sweetening), and/or perfuming agents.

[733] "Parenteral administration" includes subcutaneous injections, intravenous injections, intramuscular injections, intrasternal injections, and infusion. Injectable preparations (*e.g.*, sterile injectable aqueous or oleaginous suspensions) can be formulated according to the known art using suitable dispersing, wetting agents, and/or suspending agents. Acceptable vehicles and solvents include, for example, water, 1,3-butanediol, Ringer's solution, isotonic sodium chloride solution, bland fixed oils (*e.g.*, synthetic mono- or diglycerides), fatty acids (*e.g.*, oleic acid), dimethyl acetamide, surfactants (*e.g.*, ionic and non-ionic detergents), and/or polyethylene glycols.

[734] Formulations for parenteral administration may, for example, be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The hydroxamates or salts thereof can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, com oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers.

[735] Suppositories for rectal administration can be prepared by, for example, mixing the drug with a suitable nonirritating excipient that is solid at ordinary temperatures, but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, such as cocoa butter; synthetic mono-, di-, or triglycerides; fatty acids; and/or polyethylene glycols

[736] "Topical administration" includes the use of transdermal administration, such as transdermal patches or iontophoresis devices.

[737] Other adjuvants and modes of administration well-known in the pharmaceutical art may also be used.

E. Definitions

[738] The term "alkyl" (alone or in combination with another term(s)) means a straight-or branched-chain saturated hydrocarbyl typically containing from 1 to about 20 carbon atoms, more typically from 1 to about 8 carbon atoms, and even more typically from 1 to about 6 carbon atoms. Examples of such substituents include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, and the like.

[739] The term "alkenyl" (alone or in combination with another term(s)) means a straight- or branched-chain hydrocarbyl containing one or more double bonds and typically from 2 to about 20 carbon atoms, more typically from about 2 to about 8 carbon atoms, and even more typically from about 2 to about 6 carbon atoms. Examples of such substituents include ethenyl (vinyl); 2-propenyl; 3-propenyl; 1,4-pentadienyl; 1,4-butadienyl; 1-butenyl; 2-butenyl; 3-butenyl; decenyl; and the like.

[740] The term "alkynyl" (alone or in combination with another term(s)) means a straight- or branched-chain hydrocarbyl containing one or more triple bonds and typically from 2 to about 20 carbon atoms, more typically from about 2 to about 8 carbon atoms, and even more typically from about 2 to about 6 carbon atoms. Examples of such substituents include ethynyl, 2-propynyl, 3-propynyl, decynyl, 1-butynyl, 2-butynyl, 3-butynyl, and the like.

[741] The term "carbocyclyl" (alone or in combination with another term(s)) means a saturated cyclic (*i.e.*, "cycloalkyl"), partially saturated cyclic, or aryl hydrocarbyl containing from 3 to 14 carbon ring atoms ("ring atoms" are the atoms bound together to

form the ring or rings of a cyclic group). A carbocyclyl may be a single ring, which typically contains from 3 to 6 ring atoms. Examples of such single-ring carbocyclyls include cyclopropanyl, cyclobutanyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl. A carbocyclyl alternatively may be 2 or 3 rings fused together, such as naphthalenyl, tetrahydronaphthalenyl (also known as "tetralinyl"), indenyl, isoindenyl, indanyl, bicyclodecanyl, anthracenyl, phenanthrene, benzonaphthenyl (also known as "phenalenyl"), fluoreneyl, decalinyl, and norpinanyl.

[742] The term "cycloalkyl" (alone or in combination with another term(s)) means a saturated cyclic hydrocarbyl containing from 3 to 14 carbon ring atoms. A cycloalkyl may be a single carbon ring, which typically contains from 3 to 6 carbon ring atoms. Examples of single-ring cycloalkyls include cyclopropyl (or "cyclopropanyl"), cyclobutyl (or "cyclobutanyl"), cyclopentyl (or "cyclopentanyl"), and cyclohexyl (or "cyclohexanyl"). A cycloalkyl alternatively may be 2 or 3 carbon rings fused together, such as, decalinyl or norpinanyl.

[743] The term "aryl" (alone or in combination with another term(s)) means an aromatic carbocyclyl containing from 6 to 14 carbon ring atoms. Examples of aryls include phenyl, naphthalenyl, and indenyl.

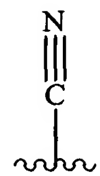
[744] In some instances, the number of carbon atoms in a hydrocarbyl (*e.g.*, alkyl, alkenyl, alkynyl, or cycloalkyl) is indicated by the prefix "C_x-C_y-", wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, "C_1-C_6-alkyl" refers to an alkyl containing from 1 to 6 carbon atoms. Illustrating further, C_3-C_6-cycloalkyl means a saturated hydrocarbyl ring containing from 3 to 6 carbon ring atoms.

[745] The term "hydrogen" (alone or in combination with another term(s)) means a hydrogen radical, and may be depicted as -H.

[746] The term "hydroxy" (alone or in combination with another term(s)) means -OH.

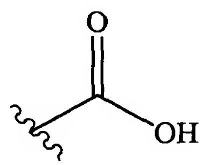
[747] The term "nitro" (alone or in combination with another term(s)) means $-NO_2$.

[748] The term "cyano" (alone or in combination with another term(s)) means -CN, which also may be depicted as:



[749] The term "keto" (alone or in combination with another term(s)) means an oxo radical, and may be depicted as =O.

[750] The term "carboxy" (alone or in combination with another term(s)) means -C(O)-OH, which also may be depicted as:



[751] The term "amino" (alone or in combination with another term(s)) means $-NH_2$. The term "monosubstituted amino" (alone or in combination with another term(s)) means an amino wherein one of the hydrogen radicals is replaced by a non-hydrogen substituent. The term "disubstituted amino" (alone or in combination with another term(s)) means an amino wherein both of the hydrogen atoms are replaced by non-hydrogen substituents, which may be identical or different.

[752] The term "halogen" (alone or in combination with another term(s)) means a fluorine radical (which may be depicted as -F), chlorine radical (which may be depicted as -Cl), bromine radical (which may be depicted as -Br), or iodine radical (which may be depicted as -I). Typically, a fluorine radical or chlorine radical is preferred, with a fluorine radical often being particularly preferred.

[753] If a substituent is described as being "substituted", a non-hydrogen radical is in the place of a hydrogen radical on a carbon or nitrogen of the substituent. Thus, for example, a substituted alkyl substituent is an alkyl substituent wherein at least one non-hydrogen radical is in the place of a hydrogen radical on the alkyl substituent. To illustrate, monofluoroalkyl is alkyl substituted with a fluoro radical, and difluoroalkyl is alkyl substituted with two fluoro radicals. It should be recognized that if there are more than one substitutions on a substituent, each non-hydrogen radical may be identical or different (unless otherwise stated).

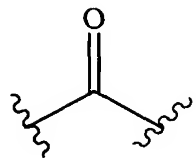
[754] If a substituent is described as being "optionally substituted", the substituent may be either (1) substituted, or (2) not substituted.

[755] This specification uses the terms "substituent" and "radical" interchangeably.

[756] The prefix "halo" indicates that the substituent to which the prefix is attached is substituted with one or more independently selected halogen radicals. For example, haloalkyl means an alkyl wherein at least one hydrogen radical is replaced with a halogen radical. Examples of haloalkyls include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl, and the like. Illustrating further, "haloalkoxy" means an alkoxy wherein at least one hydrogen radical is replaced by a halogen radical. Examples of haloalkoxy substituents include chloromethoxy, 1-bromoethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy (also known as "perfluoromethyoxy"), 1,1,1,-trifluoroethoxy, and the like. It should be recognized that if a substituent is substituted by more than one halogen radical, those halogen radicals may be identical or different (unless stated otherwise).

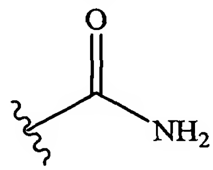
[757] The prefix "perhalo" indicates that every hydrogen radical on the substituent to which the prefix is attached is replaced with independently selected halogen radicals, *i.e.*, each hydrogen radical on the substituent is replaced with a halogen radical. If all the halogen radicals are identical, the prefix typically will identify the halogen radical. Thus, for example, the term "perfluoro" means that every hydrogen radical on the substituent to which the prefix is attached is substituted with a fluorine radical. To illustrate, the term "perfluoroalkyl" means an alkyl wherein a fluorine radical is in the place of each hydrogen radical. Examples of perfluoroalkyl substituents include trifluoromethyl ($-CF_3$), perfluorobutyl, perfluoroisopropyl, perfluorododecyl, perfluorodecyl, and the like. To illustrate further, the term "perfluoroalkoxy" means an alkoxy wherein each hydrogen radical is replaced with a fluorine radical. Examples of perfluoroalkoxy substituents include trifluoromethoxy ($-O-CF_3$), perfluorobutoxy, perfluoroisopropoxy, perfluorododecoxy, perfluorodecoxy, and the like.

[758] The term "carbonyl" (alone or in combination with another term(s)) means -C(O)-, which also may be depicted as:



This term also is intended to encompass a hydrated carbonyl substituent, *i.e.*, $-C(OH)_2-$.

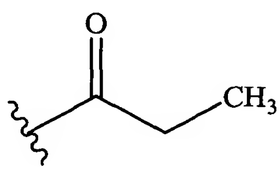
[759] The term "aminocarbonyl" (alone or in combination with another term(s)) means $-C(O)-NH_2$, which also may be depicted as:



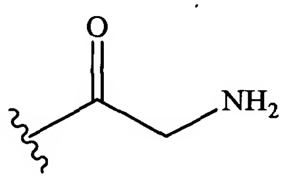
[760] The term "oxy" (alone or in combination with another term(s)) means an ether substituent, and may be depicted as -O-.

[761] The term "alkoxy" (alone or in combination with another term(s)) means an alkylether, *i.e.*, -O-alkyl. Examples of such a substituent include methoxy ($-O-CH_3$), ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

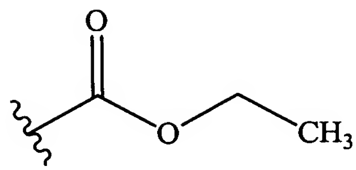
[762] The term "alkylcarbonyl" (alone or in combination with another term(s)) means -C(O)-alkyl. For example, "ethylcarbonyl" may be depicted as:



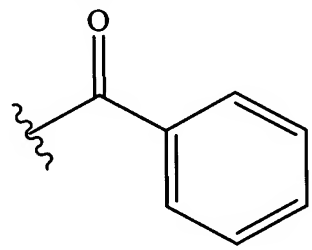
[763] The term "aminoalkylcarbonyl" (alone or in combination with another term(s)) means $-C(O)-alkyl-NH_2$. For example, "aminomethylcarbonyl" may be depicted as:



[764] The term "alkoxycarbonyl" (alone or in combination with another term(s)) means -C(O)-O-alkyl. For example, "ethoxycarbonyl" may be depicted as:

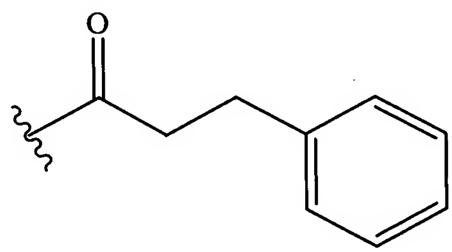


[765] The term "carbocyclylcarbonyl" (alone or in combination with another term(s)) means -C(O)-carbocyclyl. For example, "phenylcarbonyl" may be depicted as:



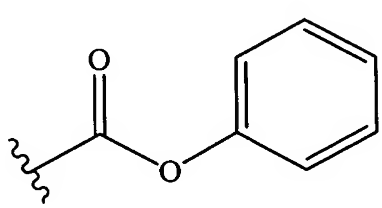
Similarly, the term "heterocyclylcarbonyl" (alone or in combination with another term(s)) means -C(O)-heterocyclyl.

[766] The term "carbocyclylalkylcarbonyl" (alone or in combination with another term(s)) means -C(O)-alkyl-carbocyclyl. For example, "phenylethylcarbonyl" may be depicted as:

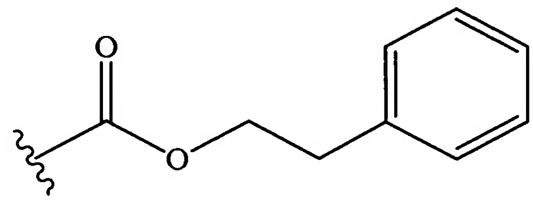


Similarly, the term "heterocyclylalkylcarbonyl" (alone or in combination with another term(s)) means -C(O)-alkyl-heterocyclyl.

[767] The term "carbocyclyloxycarbonyl" (alone or in combination with another term(s)) means -C(O)-O-carbocyclyl. For example, "phenyloxycarbonyl" may be depicted as:



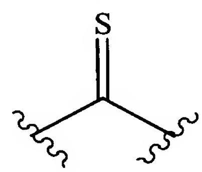
[768] The term "carbocyclylalkoxycarbonyl" (alone or in combination with another term(s)) means -C(O)-O-alkyl-carbocyclyl. For example, "phenylethoxycarbonyl" may be depicted as:



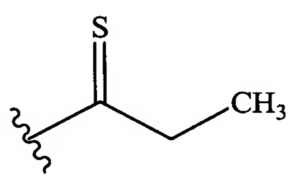
[769] The term "thio" or "thia" (alone or in combination with another term(s)) means a thiaether, *i.e.*, an ether substituent wherein a divalent sulfur atom is in the place of the ether oxygen atom. Such a substituent may be depicted as -S-. This, for example, "alkyl-thio-alkyl" means alkyl-S-alkyl.

[770] The term "thiol" or "sulfhydryl" (alone or in combination with another term(s)) means a sulfhydryl, and may be depicted as -SH.

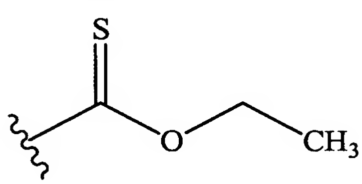
[771] The term "(thiocarbonyl)" (alone or in combination with another term(s)) means a carbonyl wherein the oxygen atom has been replaced with a sulfur. Such a substituent may be depicted as -C(S)-, and also may be depicted as:



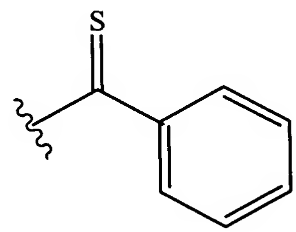
[772] The term "alkyl(thiocarbonyl)" (alone or in combination with another term(s)) means -C(S)-alkyl. For example, "ethyl(thiocarbonyl)" may be depicted as:



[773] The term "alkoxy(thiocarbonyl)" (alone or in combination with another term(s)) means -C(S)-O-alkyl. For example, "ethoxy(thiocarbonyl)" may be depicted as:

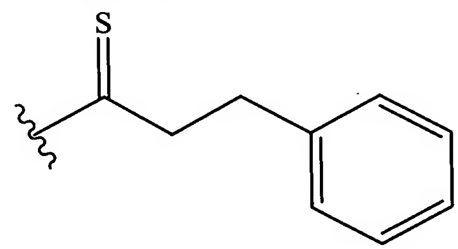


[774] The term "carbocyclyl(thiocarbonyl)" (alone or in combination with another term(s)) means -C(S)-carbocyclyl. For example, "phenyl(thiocarbonyl)" may be depicted as:



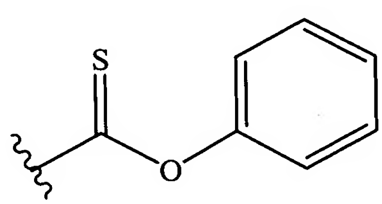
Similarly, the term "heterocyclyl(thiocarbonyl)" (alone or in combination with another term(s)) means -C(S)-heterocyclyl.

[775] The term "carbocyclylalkyl(thiocarbonyl)" (alone or in combination with another term(s)) means -C(S)-alkyl-carbocyclyl. For example, "phenylethyl(thiocarbonyl)" may be depicted as:

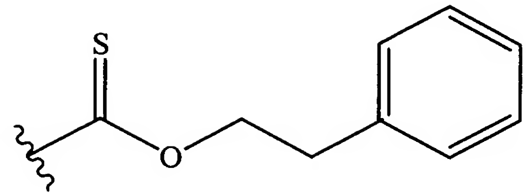


Similarly, the term "heterocyclylalkyl(thiocarbonyl)" (alone or in combination with another term(s)) means -C(S)-alkyl-heterocyclyl.

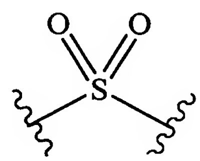
[776] The term "carbocyclyloxy(thiocarbonyl)" (alone or in combination with another term(s)) means -C(S)-O-carbocyclyl. For example, "phenyloxy(thiocarbonyl)" may be depicted as:



[777] The term "carbocyclylalkoxy(thiocarbonyl)" (alone or in combination with another term(s)) means -C(S)-O-alkyl-carbocyclyl. For example, "phenylethoxy(thiocarbonyl)" may be depicted as:

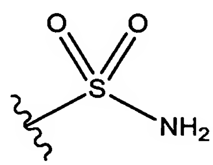


[778] The term "sulfonyl" (alone or in combination with another term(s)) means $-S(O)_2-$, which also may be depicted as:

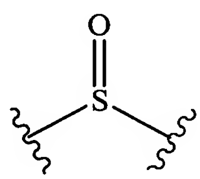


Thus, for example, "alkyl-sulfonyl-alkyl" means alkyl-$S(O)_2$-alkyl.

[779] The term "aminosulfonyl" (alone or in combination with another term(s)) means $-S(O)_2-NH_2$, which also may be depicted as:



[780] The term "sulfoxido" (alone or in combination with another term(s)) means -S(O)-, which also may be depicted as:



Thus, for example, "alkyl-sulfoxido-alkyl" means alkyl-S(O)-alkyl.

[781] The term "heterocyclyl" (alone or in combination with another term(s)) means a saturated (*i.e.*, "heterocycloalkyl"), partially saturated, or aryl (*i.e.*, "heteroaryl") ring structure containing a total of 3 to 14 ring atoms. At least one of the ring atoms is a heteroatom (*i.e.*, oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur.

[782] A heterocyclyl may be a single ring, which typically contains from 3 to 7 ring atoms, more typically from 3 to 6 ring atoms, and even more typically 5 to 6 ring atoms. Examples of single-ring heterocyclyls include furanyl, dihydrofurnayl, tetradydrofurnayl, thiophenyl (also known as "thiofuranyl"), dihydrothiophenyl,

tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl (including 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl (also known as "azoximyl"), 1,2,5-oxadiazolyl (also known as "furazanyl"), or 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl or 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, or 1,3,4-dioxazolyl), oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl (including 1,2-pyranyl or 1,4-pyranyl), dihydropyranyl, pyridinyl (also known as "azinyl"), piperidinyl, diazinyl (including pyridazinyl (also known as "1,2-diazinyl"), pyrimidinyl (also known as "1,3-diazinyl"), or pyrazinyl (also known as "1,4-diazinyl")), piperazinyl, triazinyl (including s-triazinyl (also known as "1,3,5-triazinyl"), as-triazinyl (also known 1,2,4-triazinyl), and v-triazinyl (also known as "1,2,3-triazinyl")), oxazinyl (including 1,2,3-oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl (also known as "pentoxazolyl"), 1,2,6-oxazinyl, or 1,4-oxazinyl), isoxazinyl (including o-isoxazinyl or p-isoxazinyl), oxazolidinyl, isoxazolidinyl, oxathiazinyl (including 1,2,5-oxathiazinyl or 1,2,6-oxathiazinyl), oxadiazinyl (including 1,4,2-oxadiazinyl or 1,3,5,2-oxadiazinyl), morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl.

[783] A heterocyclyl alternatively may be 2 or 3 rings fused together, such as, for example, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, or pyrido[4,3-b]-pyridinyl), and pteridinyl. Other examples of fused-ring heterocyclyls include benzo-fused heterocyclyls, such as indolyl, isoindolyl (also known as "isobenzazolyl" or "pseudoisoindolyl"), indoleninyl (also known as "pseudoindolyl"), isoindazolyl (also known as "benzpyrazolyl"), benzazinyl (including quinolinyl (also known as "1-benzazinyl") or isoquinolinyl (also known as "2-benzazinyl")), phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl (including cinnolinyl (also known as "1,2-benzodiazinyl") or quinazolinyl (also known as "1,3-benzodiazinyl")), benzopyranyl (including "chromanyl" or "isochromanyl"), benzothiopyranyl (also known as "thiochromanyl"), benzoxazolyl, indoxazinyl (also known as "benzisoxazolyl"), anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl (also known as "coumaronyl"), isobenzofuranyl, benzothienyl (also known as "benzothiophenyl",

"thionaphthenyl", or "benzothiofuranyl"), isobenzothienyl (also known as "isobenzothiophenyl", "isothionaphthenyl", or "isobenzothiofuranyl"), benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl (including 1,3,2-benzoxazinyl , 1,4,2-benzoxazinyl , 2,3,1-benzoxazinyl , or 3,1,4-benzoxazinyl), benzisoxazinyl (including 1,2-benzisoxazinyl or 1,4-benzisoxazinyl), tetrahydroisoquinolinyl , carbazolyl, xanthenyl, and acridinyl.

[784] The term "2-fused'ring" heterocyclyl (alone or in combination with another term(s)) means a saturated, partially saturated, or aryl heterocyclyl containing 2 fused rings. Examples of 2-fused-ring heterocyclyls include indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, and tetrahydroisoquinolinyl.

[785] The term "heteroaryl" (alone or in combination with another term(s)) means an aromatic heterocyclyl containing from 5 to 14 ring atoms. A heteroaryl may be a single ring or 2 or 3 fused rings. Examples of heteroaryl substituents include 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl, and pyridazinyl; 5-membered ring substituents such as 1,3,5-, 1,2,4- or 1,2,3-tiiazinyl, imidazyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl; 6/5-membered fused ring substituents such as benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl, and anthranilyl; and 6/6-membered fused rings such as 1,2-, 1,4-, 2,3- and 2, 1-benzopyronyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and 1,4-benzoxazinyl.

[786] A carbocyclyl or heterocyclyl can optionally be substituted with, for example, one or more substituents independently selected from the group consisting of halogen, hydroxy, carboxy, keto, alkyl, alkoxy, alkoxyalkyl, alkylcarbonyl (also known as "alkanoyl"), aryl, arylalkyl, arylalkoxy, arylalkoxyalkyl, arylalkoxycarbonyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkoxy, cycloalkylalkoxyalkyl, and cycloalkylalkoxycarbonyl. More typically, a carbocyclyl or heterocyclyl may optionally be substituted with, for

example, one or more substituents independently selected from the group consisting of halogen, -OH, -C(O)-OH, keto, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylcarbonyl, aryl, aryl-C_1-C_6-alkyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkoxy-C_1-C_6-alkyl, aryl-C_1-C_6-alkoxycarbonyl, cycloalkyl, cycloalkyl-C_1-C_6-alkyl, cycloalkyl-C_1-C_6-alkoxy, cycloalkyl-C_1-C_6-alkoxy-C_1-C_6-alkyl, and cycloalkyl-C_1-C_6-alkoxycarbonyl. The alkyl, alkoxy, alkoxyalkyl, alkylcarbonyl, aryl, arylalkyl, arylalkoxy, arylalkoxyalkyl, or arylalkoxycarbonyl substituent(s) may further be substituted with, for example, one or more halogen. The aryls or cycloalkyls are typically single-ring substituents containing from 3 to 6 ring atoms, and more typically from 5 to 6 ring atoms.

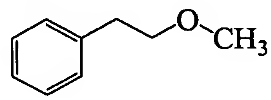
[787] An aryl or heteroaryl can optionally be substituted with, for example, one or more substituents independently selected from the group consisting of halogen, -OH, -CN, $-NO_2$, -SH, -C(O)-OH, amino, aminocarbonyl, aminoalkyl, alkyl, alkylthio, carboxyalkylthio, alkylcarbonyl, alkylcarbonyloxy, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkoxy, alkoxyalkylthio, alkoxycarbonylalkylthio, carboxyalkoxy, alkoxycarbonylalkoxy, carbocyclyl, carbocyclylalkyl, carbocyclyloxy, carbocyclylthio, carbocyclylalkylthio, carbocyclylamino, carbocyclylalkylamino, carbocyclylcarbonylamino, carbocyclylcarbonyl, carbocyclylalkyl, carbonyl, carbocyclylcarbonyloxy, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, carbocyclyloxyalkoxycarbocyclyl, carbocyclylthioalkylthiocarbocyclyl, carbocyclylthioalkoxycarbocyclyl, carbocyclyloxyalkylthiocarbocyclyl, heterocyclyl, heterocyclylalkyl, heterocyclyloxy, heterocyclylthio, heterocyclylalkylthio, heterocyclylamino, heterocyclylalkylamino, heterocyclylcarbonylamino, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, heterocyclyloxycarbonyl, heterocyclylcarbonyloxy, heterocyclylalkoxycarbonyl, heterocyclyloxyalkoxyheterocyclyl, heterocyclylthioalkylthioheterocyclyl, heterocyclylthioalkoxyheterocyclyl, and heterocyclyloxyalkylthioheterocyclyl. More typically, an aryl or heteroaryl may, for example, optionally be substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -CN, $-NO_2$, -SH, -C(O)-OH, amino, aminocarbonyl, amino-C_1-C_6-alkyl, C_1-C_6-alkyl, C_1-C_6-alkylthio, carboxy-C_1-C_6-alkylthio, C_1-C_6-alkylcarbonyl, C_1-C_6-alkylcarbonyloxy, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxycarbonyl,

C_1-C_6-alkoxycarbonyl-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkylthio, C_1-C_6-alkoxycarbonyl-C_1-C_6-alkylthio, carboxy-C_1-C_6-alkoxy, C_1-C_6-alkoxycarbonyl-C_1-C_6-alkoxy, aryl, aryl-C_1-C_6-alkyl, aryloxy, arylthio, aryl-C_1-C_6-alkylthio, arylamino, aryl-C_1-C_6-alkylamino, arylcarbonylamino, arylcarbonyl, aryl-C_1-C_6-alkylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, aryl-C_1-C_6-alkoxycarbonyl, aryloxy-C_1-C_6-alkoxyaryl, arylthio-C_1-C_6-alkylthioaryl, arylthio-C_1-C_6-alkoxyaryl, aryloxy-C_1-C_6-alkylthioaryl, cycloalkyl, cycloalkyl-C_1-C_6-alkyl, cycloalkyloxy, cycloalkylthio, cycloalkyl-C_1-C_6-alkylthio, cycloalkylamino, cycloalkyl-C_1-C_6-alkylamino, cycloalkylcarbonylamino, cycloalkylcarbonyl, cycloalkyl-C_1-C_6-alkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyloxycarbonyl, cycloalkyl-C_1-C_6-alkoxycarbonyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryloxy, heteroarylthio, heteroaryl-C_1-C_6-alkylthio, heteroarylamino, heteroaryl-C_1-C_6-alkylamino, heteroarylcarbonylamino, heteroarylcarbonyl, heteroaryl-C_1-C_6-alkylcarbonyl, heteroaryloxycarbonyl, heteroarylcarbonyloxy, and heteroaryl-C_1-C_6-alkoxycarbonyl. Here, one or more hydrogen bound to a carbon in any such substituent may, for example, optionally be replaced with halogen. In addition, the cycloalkyl, aryl, and heteroaryl are typically single-ring substituents containing 3 to 6 ring atoms, and more typically 5 or 6 ring atoms.

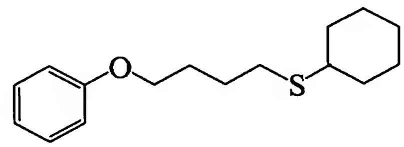
[788] A prefix attached to a multi-component substituent only applies to the first component. To illustrate, the term "alkylcycloalkyl" contains two components: alkyl and cycloalkyl. Thus, the C_1-C_6- prefix on C_1-C_6-alkylcycloalkyl means that the alkyl component of the alkylcycloalkyl contains from 1 to 6 carbon atoms; the C_1-C_6- prefix does not describe the cycloalkyl component. To illustrate further, the prefix "halo" on haloalkoxyalkyl indicates that *only* the alkoxy component of the alkoxyalkyl substituent is substituted with one or more halogen radicals. If halogen substitution may *alternatively or additionally* occur on the alkyl component, the substituent would instead be described as "halogen-substituted alkoxyalkyl" rather than "haloalkoxyalkyl." And finally, if the halogen substitution may *only* occur on the alkyl component, the substituent would instead be described as "alkoxyhaloalkyl."

[789] If substituents are described as being "independently selected" from a group, each substituent is selected independent of the other. Each substituent therefore may be identical to or different from the other substituent(s).

[790] When words are used to describe a substituent, the rightmost-described component of the substituent is the component that has the free valence. To illustrate, benzene substituted with methoxyethyl has the following structure:

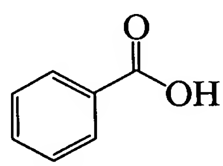


As can be seen, the ethyl is bound to the benzene, and the methoxy is the component of the substituent that is the component furthest from the benzene. As further illustration, benzene substituted with cyclohexanylthiobutoxy has the following structure:

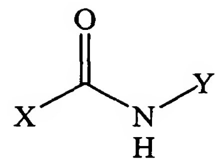


[791] When words are used to describe a linking element between two other elements of a depicted chemical structure, the rightmost-described component of the substituent is the component that is bound to the left element in the depicted structure. To illustrate, if the chemical structure is X-L-Y and L is described as methylcyclohexanylethyl, then the chemical would be X-ethyl-cyclohexanyl-methyl-Y.

[792] When a chemical formula is used to describe a substituent, the dash on the left side of the formula indicates the portion of the substituent that has the free valence. To illustrate, benzene substituted with -C(O)-OH has the following structure:



[793] When a chemical formula is used to describe a linking element between two other elements of a depicted chemical structure, the leftmost dash of the substituent indicates the portion of the substituent that is bound to the left element in the depicted structure. The rightmost dash, on the other hand, indicates the portion of the substituent that is bound to the right element in the depicted structure. To illustrate, if the depicted chemical structure is X-L-Y and L is described as -C(O)-N(H)-, then the chemical would be:



[794] The term "pharmaceutically acceptable" is used adjectivally in this patent to mean that the modified noun is appropriate for use as a pharmaceutical product or as a part of a pharmaceutical product.

[795] With reference to the use of the words "comprise" or "comprises" or "comprising" in this patent (including the claims), Applicants note that unless the context requires otherwise, those words are used on the basis and clear understanding that they are to be interpreted inclusively, rather than exclusively, and that Applicants intend each of those words to be so interpreted in construing this patent, including the claims below.

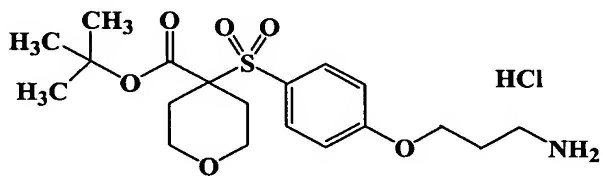
F. Compound Preparation

[796] The detailed examples below illustrate preparation of compounds and salts of this invention. Other compounds and salts of this invention may be prepared using the methods illustrated in these examples (either alone or in combination with techniques generally known in the art). Such known techniques include, for example, those disclosed in Int'l Publ. No. WO 99/25687 (PCT Patent Application No. PCT/US98/23242 published on May 27, 1999) (incorporated herein by reference). Such known techniques also include, for example, those disclosed in Int'l Publ. No. WO 00/50396 (PCT Patent Application No. PCT/US00/02518 published on August 31, 2000) (incorporated herein by reference). Such known techniques further include, for example, those disclosed in Int'l Publ. No. WO 00/69821 (PCT Patent Application No. PCT/US00/06719 published on November 23, 2000) (incorporated herein by reference).

EXAMPLES

[797] The following examples are merely illustrative, and not limiting to the remainder of this disclosure in any way.

[798] **Example 1. Preparation of 4-[[4-(3-aminopropoxy)-phenyl]sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid 1,1-dimethylethyl ester, monohydrochloride.**



[799] **Part A.** To a solution of t-butylchloroacetate (67 g, 0.44 mol) and 4-fluorothiophenol (50 g, 0.40 mol) in N,N-dimethylformamide (1 L) was added potassium carbonate (62 g, 0.45 mol), followed by dimethylaminopyridine (2 g, 0.02 mol). The mixture was stirred at ambient temperature overnight under nitrogen. Once HPLC showed that the reaction was complete, the mixture was poured into stirring 10% aqueous HCl (1 L) and extracted with ethyl acetate (4x). The combined organic layers were washed with water (2x), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford 112 g (100^+% crude yield) of a brown oil. ^{1}H NMR confirmed the desired sulfide with no disulfide formation. This material was used without further purification.

[800] **Part B.** To a solution of the product from **Part A** (approximately 108g, 0.45 mol) in tetrahydrofuran (400 ml) was added water (700 ml), followed by Oxone™ (600 g, 0.98 mol). The reaction mixture was stirred overnight. Once HPLC showed completion, the reaction mixture was filtered to remove excess Oxone™, and the mother liquor was then extracted with ethyl acetate (3x). The combined organic layers were washed with water (2x), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford 78.3 g (64% crude yield) of a yellow oil. Both ^{19}F and ^{1}H NMR were consistent with the desired sulfone with no starting material remaining. This material was used without further purification.

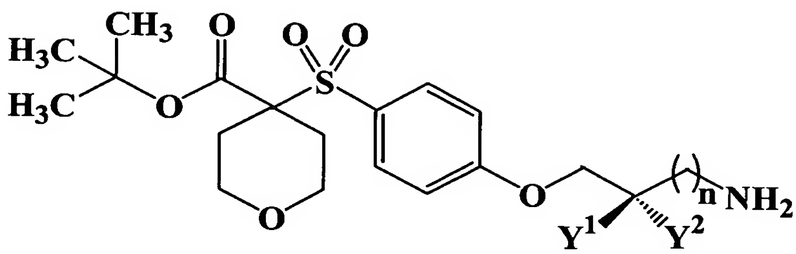
[801] **Part C.** To a solution of the product from **Part B** (78 g, 0.28 mol) in N,N-dimethylacetamide (300 ml) was added potassium carbonate (86 g, 0.62 mol). After stirring for 5 min, 2,2'- (dibromoethyl) ether (79 g, 0.34 mol) was added, followed by 4-

dimethylaminopyridine (1.7 g, 0.014 mol) and tetrabutylammonium bromide (4.5 g, 0.14 mol). The reaction mixture was stirred overnight via a mechanical stirrer. Once HPLC showed completion, the reaction mixture was slowly dumped into stirring 10% aqueous HCl (1 L). The resulting yellow solid was collected and washed with hexanes to afford 84 g (86%) of a yellow solid. ^{1}H NMR confirmed the desired product.

[802] **Part D.** To a solution of the product from **Part C** (19.8 g, 57.5 mmol) and t-butyl-N-(3-hydroxypropyl) carbamate (11.1 g, 63.3 mmol) in anhydrous N,N-dimethylformamide (300 mL) at 0°C was added sodium hydride (2.8 g, 69.0 mmol; 60% dispersion in mineral oil). After 18 hr, the reaction was quenched with water and concentrated *in vacuo*. The oily residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The layers were separated, and the organic layer was washed with brine (3X), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The oily residue was taken up in acetonitrile and again concentrated *in vacuo*. The resulting solid was triturated with diethyl ether, and 15.3 g (53%) of the pure desired product was collected as a white powder. ESMS m/z = 522 $[M+Na]^+$. The filtrate contained 11.6 g of material which was shown by HPLC to be 55% product. This material could be purified by flash chromatography to obtain more material if desired.

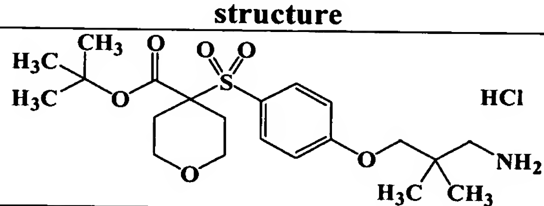
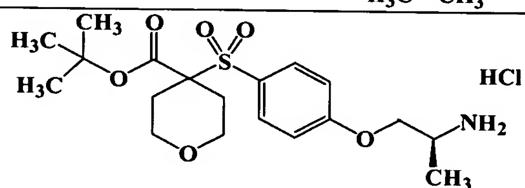
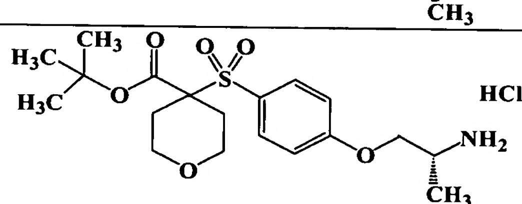
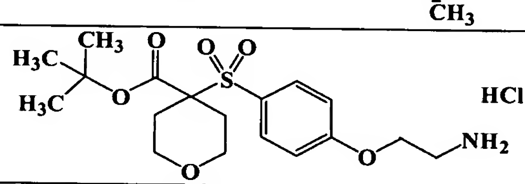
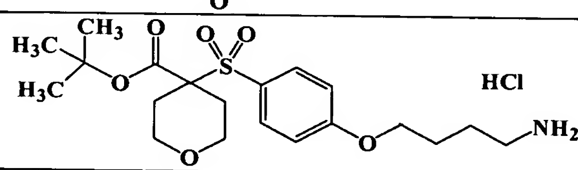
[803] **Part E.** The product from **Part D** (15.3 g, 30.6 mmol) was taken up in 4N HCl in dioxane (17 mL). After 1 hr, HPLC indicated incomplete reaction, so additional 4N HCl in dioxane (2 mL) was added. After 20 min, the reaction mixture was slowly added to rapidly stirring diethyl ether (400 mL). The resulting oily solid was rinsed with more diethyl ether then dissolved in acetonitrile and concentrated *in vacuo*. 12.3 g (92%) of the desired hydrochloride salt was obtained as a white solid. ESMS m/z = 400 $[M+H]^+$.

[804] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-A. Such compounds include, for example, those summarized in Table 1.

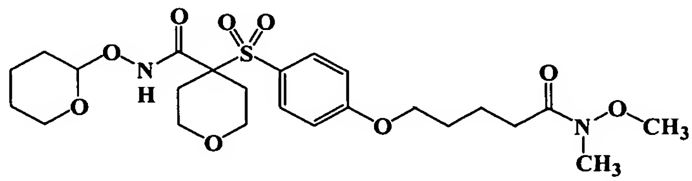


EX-A

Table 1

Ex #	structure	n	Y^1	Y^2	ESMS m/z
2		1	CH_3	CH_3	428 $(M+H)^+$
3		0	CH_3	H	422 $[M+Na]^+$
4		0	H	CH_3	422 $[M+Na]^+$
5		0	H	H	408 $[M+Na]^+$
6		2	H	H	414 $(M+H)^+$

[805] **Example 7. Preparation of tetrahydro-4-[[4-[[5-(methoxy-methylamino)-5-oxopentyl]oxy] phenyl]sulfonyl]-N-(tetrahydro-2H-pyran-2-yl)oxy]-2H-pyran-4-carboxamide**



[806] **Part A.** To a solution of 5-benzyloxy-1-pentanol (32.6 g, 168 mmol) in anhydrous N,N-dimethylformamide (150 mL) at 0°C was added sodium hydride (7.7 g, 192 mmol, 60% dispersion in mineral oil). After 15 min, the reaction mixture was allowed to warm to 20°C, and then re-cooled to 0°C. A solution of 4-[(4-fluorophenyl)sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (55.1 g, 160 mmol, as prepared in **Example 1, Part C**) in anhydrous N, N-dimethylformamide (100 mL) was added, and the cooling bath removed. After 4 hr, the reaction was concentrated *in vacuo*. The oily residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was back extracted with ethyl acetate (2X). The combined extracts were washed with 5% potassium hydrogensulfate, water, and brine (3X); dried over magnesium sulfate; filtered; and concentrated *in vacuo*. The resulting opaque oil solidified upon standing, and was subsequently purified by column chromatography using 10-20% ethyl acetate/ hexanes to afford 67.6 g (81%) of the desired product as a white solid. ESMS m/z = 541 $[M+Na]^+$.

[807] **Part B.** The product from **Part A** (20.0 g, 38.6 mmol) was dissolved in tetrahydrofuran (80 mL) in a small Fisher/Porter bottle. After purging with a stream of nitrogen for 5 min, the reaction was charged with 5% palladium on carbon catalyst (4.0 g, Degussa E101 NO/W, 50% water) and pressurized to roughly ~80 psi with hydrogen. After 1.5 hr, hydrogen uptake had ceased and HPLC analysis indicated the reaction was complete. The reaction was filtered through a bed of celite and the filtrate was concentrated to yield 17.2 g (100%) of the desired alcohol as a viscous oil. This material was used without further purification.

[808] **Part C.** The product from **Part B** (16.5 g, 38.6 mmol) was dissolved in acetonitrile (80 mL). The reaction mixture was treated with carbon tetrachloride (80 mL),

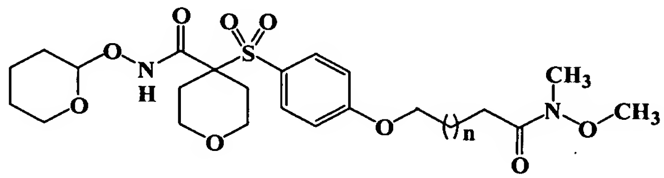
water (120 mL), then sodium periodate (24.7 g, 115.7 mmol), and finally ruthenium trichloride (180 mg, 0.9 mmol). After 1 hr, HPLC analysis indicated that the reaction was complete. The reaction mixture was diluted with methylene chloride (300 mL), and the solids were removed by gravity filtration. The layers were separated, and the aqueous layer was extracted with methylene chloride (3X). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to yield a blue solid. This was redissolved in tetrahydrofuran, slurried with activated carbon, filtered, and concentrated *in vacuo* to yield 17.1 g (100%) of an off-white solid. ^{1}HNMR was consistent with the desired product. This material was used without further purification.

[809] **Part D.** To a solution of the product from **Part C** (17.1 g, 38.6 mmol) in N,N-dimethylformamide (160 ml) was added 1-hydroxybenzotriazole (7.8g, 57.9 mmol), and then 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (10.3 g, 54.0 mmol). After 1.5 hr, N,O-dimethylhydroxylamine HCl (11.3 g, 115.7 mmol) and triethylamine (32.2 ml, 231.4 mmol) were added. The reaction mixture was left stirring at ambient temperature overnight. The mixture was concentrated, and the residue partitioned between ethyl acetate and saturated sodium bicarbonate solution. The aqueous layer was back extracted with ethyl acetate (2X), and the combined organic layers were washed with 5% potassium hydrogensulfate solution, water, and brine (3X), then dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude solid was purified by column chromatography using 50% ethyl acetate/hexanes, and 14.7 g (79%) of the desired weinreb amide was obtained as an off-white solid. ESMS m/z = 508 $[M+Na]^+$.

[810] **Part E.** The product from **Part D** (6.24 g, 12.85 mmol) was taken up in neat trifluoroacetic acid (50 mL). After 1.5 hr, the trifluoroacetic acid was removed *in vacuo* at 50°C to give the free acid as a syrupy oil. ESMS m/z = 430 $[M+H]^+$. To a solution of this material in anhydrous N,N-dimethylformamide (25 mL) was added 1-hydroxybenzotriazole (2.14 g, 15.88 mmol), tetrahydropyranhydroxylamine (4.64 g, 39.72 mmol), and triethylamine (5.5 mL, 39.72 mmol), followed by 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (3.35 g, 15.83 mmol). The reaction mixture was heated at 40°C for 3.5 hr, and then cooled to ambient temperature and stirred overnight. The reaction mixture was concentrated *in vacuo* at 60°C. The residue was taken up in ethyl acetate, washed with saturated sodium bicarbonate solution (2X) and brine (3X), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 8 g of a syrup.

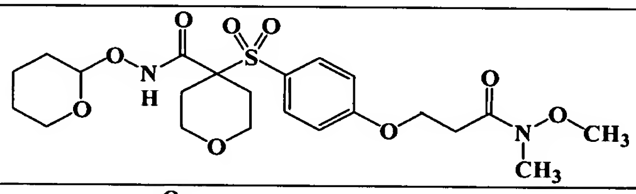
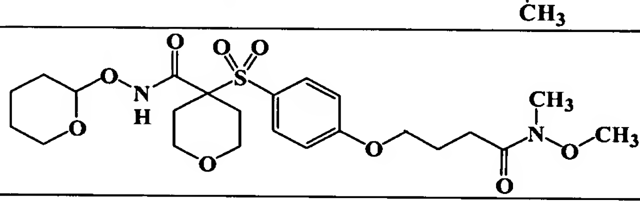
The crude material was purified by flash chromatography using 50-100% ethyl acetate/hexanes to give the title compound as a white solid. ESMS m/z = 529 [M+H]$^+$. HRMS calculated for $C_{24}H_{36}N_2O_9S$: 529. 2220 [M+H]$^+$, found: 529.2210 .

[811] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-B. Such compounds include, for example, the compound summarized in Table 2.

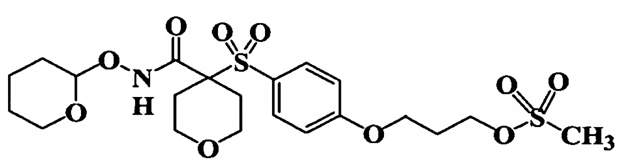


EX-B

Table 2

Ex #	structure	n	Calcd Mass	Observed Mass
8		0	518.2172	518.2176
9		1	532.2329	532.2307

[812] **Example 10: Preparation of tetrahydro-4-[[4-[3-[(methyl-sulfonyl)oxy]propoxy]phenyl)sulfonyl]-N-[(tetrahydro-2H pyran-2-yl)oxy]-2H-pyran-4-carboxamide**



[813] **Part A.** To a solution of 4-[(4-fluorophenyl)sulfonyl]-tetrahydro-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (5.0 g, 14.5 mmol, as prepared in **Example 1, Part C**) and 3-benzyloxy-l-propanol (2.3 mL, 14.5 mmol) in N,N-dimethylformamide (50 mL) at 0°C was added NaH (696 mg, 17.4 mmol, 60% dispersion

in mineral oil). The solution was stirred at ambient temperature for 5 hr. The reaction was quenched with water, and then partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 7.89 g (quantitative yield) of the benzyl ether as a yellow oil. (ESMS m/z = 435 $[M- tBu]^+$.

[814] **Part B.** The benzyl ether of **Part A** (4.39 g, 8.94 mmol) was hydrolized in 1:1 trifluoroacetic acid:methylene chloride (50 mL). The solution was concentrated *in vacuo* to provide 3.69 g (950) of the free acid as a crude white solid. ESMS m/z = 452 $[M+NH4]^+$. This material was used without purification.

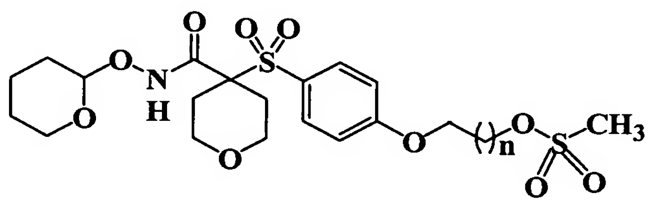
[815] **Part C.** To a solution of the crude acid of **Part B** (3.60 g, 8.29 mmol) in N,N-dimethylformamide (40 mL) was added 1-hydroxybenzotriazole (1.34 g, 9.95 mmol), triethylamine (3.5 mL, 24.9 mmol), and tetrahydropyranhydroxylamine (2.91 g, 24.9 mmol). After 30 min, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.23 g, 11.6 mmol) was added. The solution was stirred for 18 hr at ambient temperature. The solution was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was washed with saturated sodium bicarbonate solution and brine, and then dried over sodium sulfate. Purification by flash chromatography using ethyl acetate/hexanes provided 3.71 g (84 0) of the protected hydroxamate as a crude oil. ESMS m/z = 551 $(M+NH4)^+$. HRMS calculated for $C_{27}H_{35}NO_8S$ NH_4: 551.2427 $(M+NH4)^+$. Found: 551 .2418.

[816] **Part D.** The benzyl ether of **Part C** (3.52 g, 6.6 mmol) was hydrogenated over 10% palladium/carbon (3.31g) in methanol with ammonium formate (2.5 g, 39.6 mmol) as the hydrogen source added in 3 portions and heated at reflux. The solution was filtered through celite and concentrated *in vacuo* to provided 2.89 g (98 %) of the alcohol as a colorless oil. ESMS m/z = 442 $[M-H]^+$. This material was used without purification.

[817] **Part E.** To a solution of the protected hydroxamate of **Part D** (2.57 g, 5.8 mmol) in methylene chloride (25 mL) was added triethylamine (2.5 mL, 18.8 mmol). The solution was cooled to 0°C, and methylsulfonyl chloride (1.25 mL, 16.0 mmol) was added. After 18 hr, the reaction was washed with water, 10% citric acid, 5% sodium bicarbonate solution, and brine, and then dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexanes) provided the title compound as a colorless oil (1.48 g, 49 0). ESMS

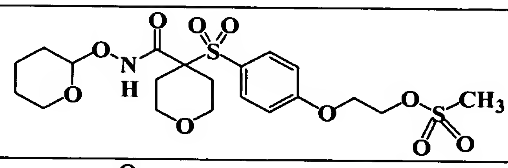
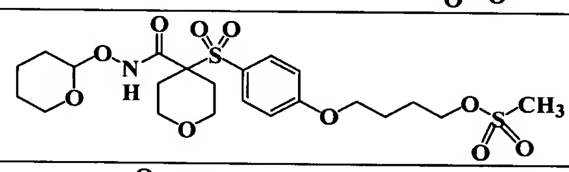
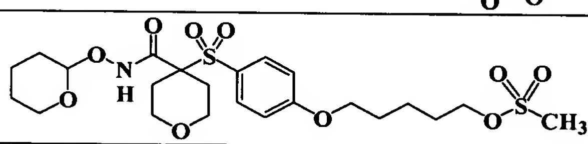
m/z = 544 $(M+Na)^+$. HRMS calculated for $C_{21}H_{31}NO_{10}S_2$ NH_4: 539. 1733 $(M+NH_4)^+$. Found: 539.1709.

[818] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-C. Such compounds include, for example, the compounds summarized in Table 3.

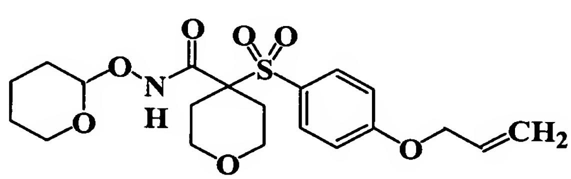


EX-C

Table 3

Ex #	structure	n	Calcd Mass	Observed Mass
11		1	525.1517	525.1561
12		3	558.1444	558.1429
13		4	572.16	572.1583

[819] **Example 14. Preparation of (tetrahydro-4-[[4-(2-propenyloxy)phenyl]sulfonyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-pyran-4-carboxamide**



[820] **Part A.** To a solution of sodium (8.97 g, 390 mmol) in methanol (1 L) at 0°C were added 4-fluorothiophenol (50 g, 390 mmol) and methyl chloroacetate (34.2 mL,

390 mmol). After stirring at ambient temperature for 4 hr, the solution was filtered to remove salts, and the filtrate was concentrated *in vacuo* to provide 75.85 g (970) for the desired sulfide as a colorless oil.

[821] **Part B.** To a solution of the product from **Part A** (75.85 g, 380 mmol) in methanol (1 L) and water (100 mL) was added Oxone™ (720 g, 1.17 mmol). After 2 hr, the reaction mixture was filtered to remove the excess salts, and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in ethyl acetate and washed with water, saturated sodium bicarbonate solution, and brine, and then dried over magnesium sulfate. Concentrating *in vacuo* provided 82.74 g (94%) of the desired sulfone as a white solid.

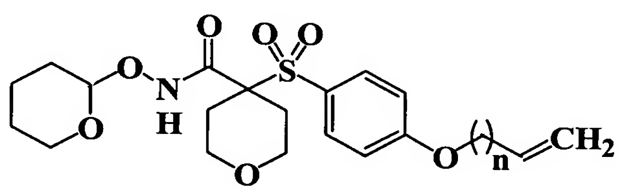
[822] **Part C.** To a solution of the product from **Part B** (28.5 g, 123 mmol) in N,N-dimethylacetamide (200 mL) were added potassium carbonate (37.3 g, 270 mmol), bis-(2-bromoethylether (19.3 mL, 147 mmol), 4-dimethylaminopyridine (750 mg, 6 mmol), and tetrabutylammonium bromide (1.98 g, 6 mmol). The resulting solution was stirred at ambient temperature for 72 hr, and then poured into 1 N HCl (300 mL). The resulting precipitate was collected by vacuum filtration. Recrystallization using ethyl acetate/hexanes provided 28.74 g (77%) of the tetrahydropyran product as a beige solid.

[823] **Part D.** To a solution of the product from **Part C** (8.0 g, 26.5 mmol) in tetrahydrofuran (250 mL) was added potassium trimethylsilonate (10.2 g, 79.5 mmol). After 1.5 hr, the reaction mixture was quenched with water, acidified to pH 2.5, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 5.78 g (76%) of the desired acid salt as a white solid.

[824] **Part E.** To a solution of the product from **Part D** (5.4 g, 18.7 mmol) in N,N-dimethylformamide (35 mL) were added 1-hydroxybenzotriazole (3.04 g, 22.5 mmol), N-methylmorpholine (6.2 mL, 56.2 mmol), tetrahydropyranhydroxylamine (6.8 g, 58.1 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.0 g, 26.2 mmol). After stirring for 3 hr at ambient temperature, the solution was concentrated *in vacuo*, and the residue partitioned between ethyl acetate and water. The organic layer was washed with 5% aqueous potassium hydrogen sulfate, water, saturated sodium bicarbonate solution, and brine; dried over sodium sulfate; filtered; and concentrated *in vacuo* to provide 6.34 g (87%) of the THP protected hydroxamate as a white solid.

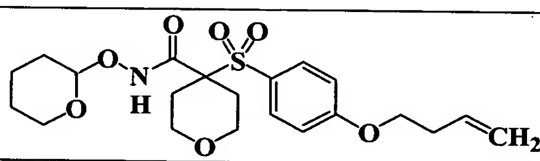
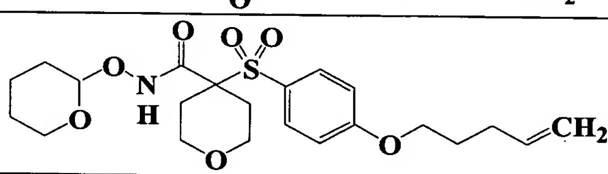
[825] **Part F.** To a solution of the product from **Part E** (1.0 g, 2.58 mmol) in dimethylsulfoxide (5 mL) was added potassium carbonate (0.89 g, 6.45 mmol) and allyl alcohol (0.35 mL, 12.9 mmol). The mixture was heated to 110°C for 72 hr. Additional allyl alcohol (0.88 mL, 13 mmol) and cesium carbonate (2.1 g, 6.45 mmol) were added, and the mixture heated at 120°C for 6 hr. After cooling to ambient temperature, the mixture was diluted with water (50 mL), and the pH adjusted to 8-9 with 1 N HCl. The aqueous layer was extracted with ethyl acetate. The organic layer was washed brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography with 15% ethyl acetate/hexanes yielded 0.67 g of pure title compound as a white solid. ESMS m/z = 426 $[M+H]^+$.

[826] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-D. Such compounds include, for example, the compounds summarized in Table 4.

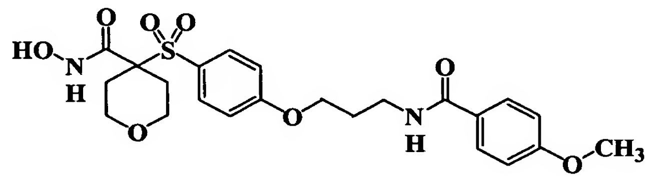


EX-D

Table 4

Ex. #	Structure	n	ESMS m/z
15		2	440 $[M+H]^+$
16		3	454 $[M+H]^+$

[827] **Example 17. Preparation of tetrahydro-N-hydroxy-4-[[4-[3-[(4-methoxybenzoyl) amino] propoxy]phenyl] sulfonyl]-2H-pyran-4-carboxamide**

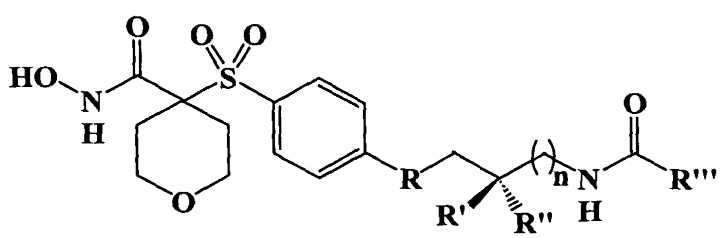


[828] **Part A.** To a solution of 4-[[4-(3-aminopropoxy)-phenyl] sulfonyl] tetrahydro-2H-pyran-4-carboxylic acid 1,1-dimethylethyl ester, monohydrochloride (507 mg, 1.27 mmol, prepared as in **Example 1**) in anhydrous N,N-dimethylformamide (5 mL) at ambient temperature was added triethylamine (215 uL, 1.54 mmol), followed immediately by panisoyl chloride (260 mg, 1.52 mmol). After 1 hr, the reaction mixture was quenched with water (~2 mL) and concentrated *in vacuo* at 60°C. The crude residue was partitioned between ethyl acetate and water. The layers were separated, and the organic layer was washed with brine (3X), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a pale yellow oil. The crude product was partially purified by flash chromatography using 80% ethyl acetate/hexanes to provide 225 mg (33%) of the desired acylated product as a clear, colorless oil. ESMS m/z = 556 $[M+Na]^+$. This material was used without further purification.

[829] **Part B.** The product from **Part A** (225 mg, 82% purity by HPLC) was taken up in neat trifluoroacetic acid (1 mL). After 3 hr, the trifluoroacetic acid was removed *in vacuo* at 50°C to give the free acid as a colorless oil. ESMS m/z = 478 $[M+H]^+$. To a solution of this material in anhydrous N,N dimethylformamide (2 mL) was added 1-hyrdoxybenzotriazole (72 mg, 0.53 mmol), N-methylmorpholine (100 uL, 0.91 mmol) and tetrahydropyranhydroxylamine (78 mg, 0.67 mmol), followed by 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (119 mg, 0.62 mmol). The reaction mixture was stirred at ambient temperature for 72 hr, and then concentrated *in vacuo* at 60°C. The residue was partitioned between ethyl acetate and water. The layers were separated, and the organic layer was washed with saturated sodium bicarbonate solution and brine (2X), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 255 mg of the desired THP protected hydroxamate as a colorless oil. ESMS m/z = 599 $[M+Na]^+$. HRMS calculated for $C_{28}H_{36}N_2O_9S$: 577.2220 $[M+H]^+$, found: 577.2215.

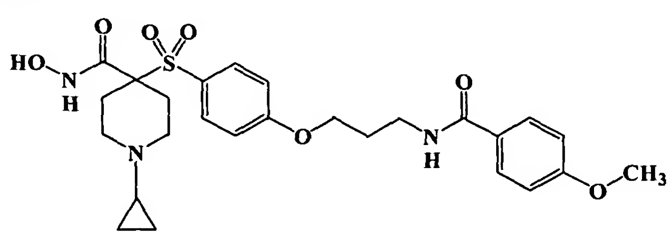
[830] **Part C.** The product from **Part B** (255 mg, 88% purity by HPLC) was dissolved in 4N HCl in dioxane (3 mL) and methanol (300 uL). After 1 hr at ambient temperature, the reaction mixture was poured into rapidly stirring diethyl ether (50 mL). A white solid was collected and dried over P_2O_5 under vacuum. The title compound was obtained as a faint pink solid. ESMS m/z = 493 $[M+H]^+$. HRMS calculated for $C_{23}H_{28}N_2O_8S$: 493.1645 $[M+H]^+$, found: 493.1636.

[831] Additional compounds (such as those having a structure corresponding to generic Formula EX-E) can be prepared by one skilled in the art using similar methods with either the t-butyl ester or free acid of 4-[[4-(3-aminopropoxy)-phenyl]sulfonyl]-tetrahydro-2H-pyran-4-carboxylic acid 1,1-dimethylethyl ester, monohydrochloride or similarly prepared starting materials. Also, one may use carboxylic acids as coupling agents in place of acid chlorides using standard peptide coupling conditions for formation of the amide bond.



EX-E

[832] **Example 18. Preparation of 1-cyclopropyl-N-hydroxy-4-[[4-[3[(4-methoxybenzoyl)amino]propoxy]phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride.**



[833] **Part A.** to a solution of ethyl isonipecotate (15.7 g, 0.1 mol) in tetrahydrofuran (100 mL) was added a solution of di-tert-butyl dicarbonate (21.8 g, 0.1 mol) in tetrahydrofuran (5 mL) dropwise over 20 min. The solution was stirred overnight at ambient temperature and concentrated *in vacuo* to yield a light oil. The oil was filtered

through silica gel using ethyl acetate/hexanes then concentrated *in vacuo* to afford 26.2 g (100%) of the desired BOC-piperidine as a clear, colorless oil.

[834] **Part B.** A solution of 4-fluorothiophenol (50.29 g, 390 mmol) in dimethyl sulfoxide (500 mL) was heated to 65°C for 6 hr. The reaction was quenched by pouring into wet ice. The resulting solid was collected by vacuum filtration to afford 34.4 g (68.9%) of the desired disulfide as a white solid.

[835] **Part C.** To a solution of the product from **Part A** (16 g, 62 mmol) in tetrahydrofuran (300 mL) cooled to -50°C was added lithium diisopropylamide (41.33 mL, 74 mmol). After being at 0°C for 1.5 hr, the product from **Part B** (15.77 g, 62 mmol) was added. The reaction mixture was stirred at ambient temperature for 20 hr, and then quenched by the addition of water. The solution was concentrated *in vacuo*, and the resulting residue was partitioned between ethyl acetate and water. The organic layer was washed with 0.5 N KOH, water, and brine. Purification by column chromatography using ethyl acetate/hexanes provided 18.0 g (75%) of the desired sulfide as an oil.

[836] **Part D.** To a solution of the product from **Part C** (16.5 g, 43 mmol) in methylene chloride (500 mL) cooled to 0°C was added 3-chloroperbenzoic acid (18.0 g, 86 mmoL). After stirring for 20 hr, the reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was washed with 10% aqueous sodium sulfite, water, and brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography using ethyl acetate/hexanes to afford 10.7 g (60%) of the desired sulfone as a solid.

[837] **Part E.** Into a solution of the product from **Part D** (10 g, 24.0 mmol) in ethyl acetate (250 mL) was bubbled HCl gas for 10 min, followed by stirring at ambient temperature for 4 hr. Concentration *in vacuo* provided 7.27 g (86%) of the amine hydrochloride salt as a white solid.

[838] **Part F.** To a solution of the product from **Part E** (10.0 g, 28.4 mmol) in methanol (100 mL) was added acetic acid (16.2 mL, 284 mmol), powdered 4A molecular sieves (9.1 g), and [(1-ethoxycyclopropyl)oxyl trimethyl silane (17.1 mL, 85.2 mmol). Sodium cyanoborohydride (4,82 g, 76.7 mmol) was then added slowly. The reaction was heated at reflux with vigorous stirring for 4.5 hr. The reaction mixture was cooled to room temperature, filtered through celite, and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic

layer was washed with saturated sodium bicarbonate solution (3X) and brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material crystallized upon standing providing 10.9 g (100%) of the alkylated amine compound as a pale yellow oily crystal. ESMS m/z = 356 $(M+H)^+$. This material was used without purification.

[839] **Part G.** The product from **Part F** (28.4 mmol) was hydrolized in tetrahydrofuran (65 mL) with LiOH (3.58 g, 85.2 mmol) in 35 mL of water at 60°C over 3 days. The solution was concentrated *in vacuo*, diluted with water, and washed with diethyl ether. The aqueous layer was acidified with 1N HCl to a pH of ~4.5, causing a white precipitate to form. The solid was collected by filtration, washed with water, and washed with ethyl acetate. After drying over silica on a high vacuum, 8.06 g (78.2 %) of the acid was obtained as a crude white solid. ESMS m/z = 328 (M+H)+. HRMS calculated for $C_{15}H_{18}NO_4SF$: 328.1019 $(M+H)^+$, found: 328.1014. This material was used without purification.

[840] **Part H.** To a solution of the crude acid of **Part G** (7.92 g, 21.8 mmol) in N,N-dimethylformamide (48 mL) was added N-methylmorpholine (12.0 mL, 109 mmol) and PyBOP (12.5 g, 24.0 mmol). After stirring 15 min, tetrahydropyranhydroxylamine (3.07 g, 26.2 mmol) was added. The solution was stirred for 22 hr at ambient temperature. The solution was diluted with water (240 mL) and extracted with ethyl acetate (3X). The combined organics were washed with saturated aqueous sodium bicarbonate solution (2X) and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to a foamy oil. The crude material was filtered through a silica plug using 1% Et_3N in ethyl acetate/hexanes to afford 7.12 g (76.60) of the protected hydroxamate as a foamy oil. ESMS m/z = 427 $(M+H)^+$. HRMS calculated for $C_{20}H_{27}N_2O_5SF$: 427.1703 $(M+H)^+$. Found: 427.1693.

[841] **Part I.** To a solution of 3-(dibenzylamino)-1-propanol (4.3 g, 16.88 mmol) in anhydrous N,N-dimethylformamide (35 mL) was added sodium hydride (1.3 g, 32.35 mmol; 60% dispersion in mineral oil). The reaction mixture was stirred for 15 min, then cooled to 0°C in an ice bath and treated with a solution of the product from **Part H** (6.0 g, 14.07 mmol) in anhydrous N,N-dimethylformamide (15 mL). After the addition was completed, the ice bath was removed and the reaction was allowed to stir at ambient temperature for 18 hr. The reaction was quenched with water and concentrated *in vacuo*. The oily residue was partitioned between ethyl acetate and saturated sodium bicarbonate

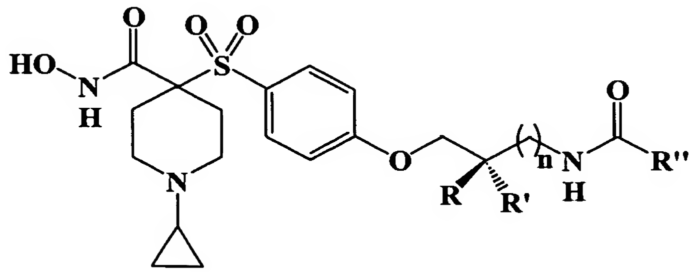
solution. The layers were separated and the aqueous layer was extracted with ethyl acetate (3X). The organic extracts were combined and washed with brine (3X), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude yellow solid was re-crystallized from hot acetonitrile. 6.5 g (70%) of the pure desired product was collected as a white powder. ESMS m/z = 662 $[M+H]^+$.

[842] **Part J.** The product from **Part I** (1.0 g, 1.51 mmol) and glacial acetic acid (0.2 g, 3.02 mmol) were slurried in methanol (15 mL) in a small Fisher/Porter bottle. After purging with a stream of nitrogen for 5 min, the reaction was charged with 20% palladium on carbon catalyst (0.5 g, Degussa E169X/W, 50% water) and pressurized to 50 psi with hydrogen. After 5 hr, hydrogen uptake had ceased, and HPLC analysis indicated the reaction was complete. The reaction was filtered through a bed of celite, and the filtrate was concentrated to yield 0.8 g (1000) of the desired mono-acetate salt as a dry, white foam. ESMS m/z = 481 $[M+H]^+$.

[843] **Part K.** To a solution of the product from **Part J** (0.7 g, 1.06 mmol) in anhydrous methylene chloride (11 mL) at ambient temperature was added triethylamine (0.73 mL, 6.35 mmol), followed by p-anisoyl chloride (0.3 g, 1.59 mmol). After 10 min, HPLC analysis showed the reaction to be complete. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer extracted with ethyl acetate (3X). The organic extracts were combined and washed with brine (3X), dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield a tan foam. The crude product was purified by flash chromatography using 60-100% [5% (2M ammonia in methanol) ethyl acetate]/hexanes to yield 0.2 g (34%) of the desired product as a dry white foam. ESMS m/z = 616 $[M+H]^+$.

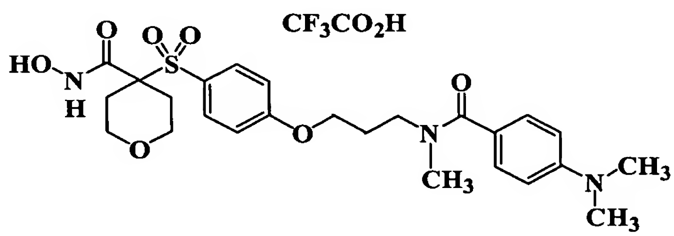
[844] **Part L.** The product from **Part K** (0 . 2 g, 0 . 34 mmol) was slurried in 4N HCl in dioxane (2 mL). After 5 min, methanol (0.2 mL) was added. After stirring for 10 min at ambient temperature, the reaction mixture was poured into rapidly stirring diethyl ether (50 mL). A white solid was collected and dried under vacuum. The title compound (as the HCl salt) was obtained as an off-white solid. ESMS m/z = 532 $[M+H]^+$. HRMS calculated for $C_{26}H_{33}N_3O_7S$: 532.2117 $[M+H]^+$, found: 532 .2098 .

[845] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-F.



EX-F

[846] **Example 19. Preparation of 4-[[4-[3-[[4-(dimethylamino)benzoyl] methylamino] propoxy] phenyl] sulfonyl] tetrahydro-N-hydroxy-2H-pyran-4-carboxamide.**

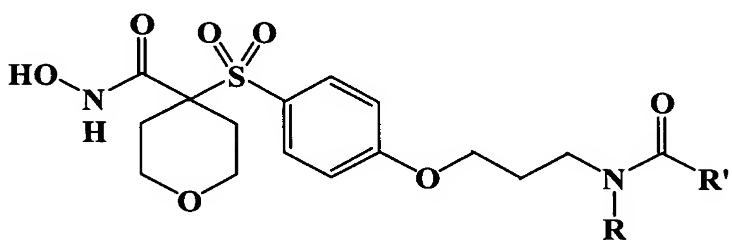


[847] **Part A.** To a solution of 4-[[4-[3-[[4(dimethylamino)-benzoyl]amino]propoxy]phenyl] sulfonyl] tetrahydro-2H-pyran-4carboxylic acid, 1,1-dimethylethyl ester (prepared as in **Example 17**) in anhydrous N,N-dimethylformamide (3 mL) was added iodomethane (61 uL, 0.98 mmol), followed by sodium hydride (24 mg, 0.59 mmol; 60% dispersion in mineral oil). After 1 hr the reaction mixture was quenched with water, washed with brine (3X), dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield the desired N-methylated product as a sticky solid. ESMS m/z = 561 $[M+H]^+$. HRMS calculated for $C_{29}H_{40}N_3O_7S$: 561.2634 $[M+H]^+$, found: 561.2628.

[848] **Part B.** The product from **Part A** (400 mg, 0.71 mmol) was taken up in neat trifluoroacetic acid (1 mL). After 1 hr, the trifluoroacetic acid was removed *in vacuo* at 60°C to give the free acid as a sticky solid. ESMS m/z = 505 $[M+H]^+$. To a solution of this material in anhydrous N,N-dimethylformamide (5 mL) was added 1-hydroxybenzotriazole (113 mg, 0.83 mmol), tetrahydropyranhydroxylamine (246 mg, 2.10

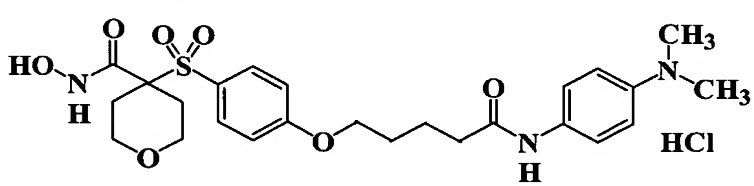
mmol), and triethylamine (390 uL, 2.8 mmol), followed by 1-(3dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (188 mg, 0.98 mmol). The reaction mixture was heated to 40°C for 4 hr, and then cooled to ambient temperature. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate solution (2X) and brine (4X), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was de-protected and simultaneously purified by reverse phase HPLC to give 59 mg of the title compound as an off-white solid. ESMS m/z = 520 $[M+H]^+$. HRMS calculated for $C_{25}H_{33}N_3O_7S$: 520.2117 $[M+H]^+$, found: 520.2120.

[849] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-G.



EX-G

[850] **Example 20. Preparation of 4-[[4-[[5-[[4-(dimethylamino)-phenyl]amino]-5-oxopentyl] oxy]phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide, monohydrochloride.**

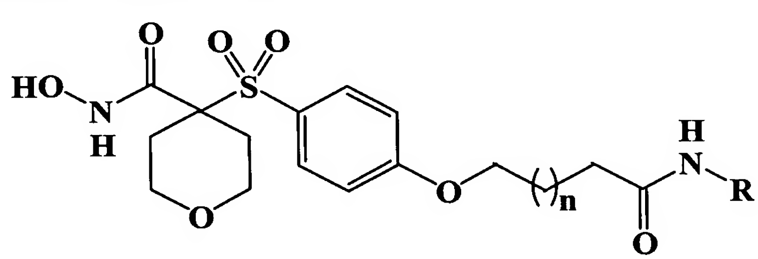


[851] **Part A.** To a solution of 4-[[4-(4-carboxybutoxy)phenyl-]sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (446 mg, 0.91 mmol, prepared as in **Example 7**) in anhydrous N,N-dimethylformamide (6 mL) was added 1-hydroxybenzotriazole (150 mg, 1.11 mmol), triethylamine (400 uL, 2.87 mmol), N,N-dimethyl-1,4-phenylenediamine (188 mg, 1.38 mmol), and finally 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (300 mg, 1.56 mmol). The reaction mixture was stirred at ambient temperature for 18 hr, and then concentrated *in*

vacuo at 60°C. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was washed with brine (2X), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the desired amide. ESMS m/z = 561 $[M+H]^+$. This material was taken up in neat trifluoroacetic acid (5 mL). After 3 hr the trifluoroacetic acid was removed *in vacuo* at 60°C to give the free acid. ESMS m/z = 505 $[M+H]^+$. To a solution of this material in anhydrous N,N-dimethylformamide (5 mL) was added 1-hydroxybenzotriazole (148 mg, 1.10 mmol), triethylamine (400 uL, 2.87 mmol), and tetrahydropyranhydroxylamine (320 mg, 2.73 mmol), followed by 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (262 mg, 1.37 mmol). The reaction mixture was stirred at ambient temperature overnight, and then partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was washed with brine (3X), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography using 80% ethyl acetate/hexanes as eluant to afford the desired THP hydroxamate. ESMS m/z = 604 $[M+H]^+$. HRMS calculated for $C_{30}H_{41}N_3O_8S$: 604.2693 $[M+H]^+$, found: 604.2709.

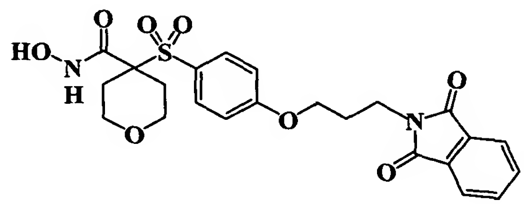
[852] **Part B.** The product from **Part A** was dissolved in 4N HCl in dioxane (5 mL) and methanol (500 uL). After 3 hr at ambient temperature the reaction mixture was poured into rapidly stirring diethyl ether (50 mL). A purplish-pink solid was collected and subsequently purified by reverse phase HPLC. The title compound was obtained as a faint pink solid 131 mg (28% from the starting acid in part A). ESMS m/z = 520 $[M+H]^+$. HRMS calculated for $C_{25}H_{33}N_3O_7SHCl$: 520.2117 $[M+H]^+$, found: 520.2127.

[853] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-H.



EX-H

[854] **Example 21. Preparation of 4-[[4-[3-(1,3-dihydro-l,3-dioxo2H-isoindol-2-yl)propoxy] phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide**



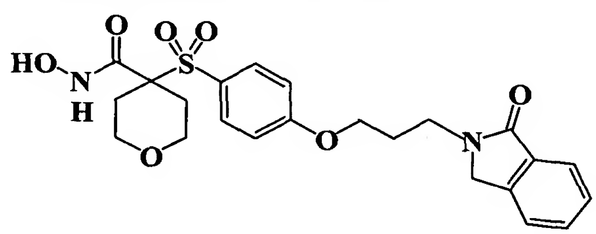
[855] **Part A.** To a solution of 4-[(4-fluorophenyl)sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid, 1,1-di-methylethyl ester (6.7 g, 19 mmol, as prepared in **Example 1, Part C**) in anhydrous N,N-dimethylformamide (40 ml) at ambient temperature was added N-(3-hydroxypropyl)phthalimide (4 g, 19 mmol), followed immediately by NaH (700 mg, 20 mmol, 60% dispersion in mineral oil). After 1.5 hr, HPLC showed less than 1% of the starting electrophile. The reaction mixture was quenched with water (60 ml). The cloudy mixture was extracted with ethyl acetate (2x100 ml). The organic layers were combined, washed with brine (1x200 ml), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a tan, viscous oil that crystallized from methanol (3.2 g, 52%). ESMS m/z = 489 $[M+H]^+$. This material was used without further purification.

[856] **Part B.** The product from **Part A** (3 g, 6 mmol) was dissolved in methylene chloride (304 ml) and trifluoroacetic acid (6 ml). After 12 hr, the mixture was concentrated *in vacuo*, and the residue was triturated with diethyl ether to form a solid which was collected and dried to afford the carboxylic acid as a beige solid (3 g, 90%). ESMS m/z = 474 [M+H]+. This material was used without further purification.

[857] **Part C.** To a solution of the product from **Part B** (3 g, 6.2 mmol) in anhydrous N,N-dimethylformamide (25 ml) was added triethylamine (2 ml, 18 mmol), followed by tetrahydropyranhydroxylamine (1 g, 8 mmol), 1-hydroxybenzotriazole (0.5 g, 3 mmol), and 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (2 g, 8 mmol). The reaction mixture was heated at 40°C for 0.5 hr. The reaction was monitored by RPHPLC. After 2 hr, the mixture was concentrated *in vacuo*, the residue was flooded with water, and the product separated as a solid. The solid was filtered, and was of sufficient purity to carry on to the next step. Mass spectral data and NMR were consistent with the desired product.

[858] **Part D.** The solid from **Part C** (3 g) was slurried in methanol (1 mL) and diethyl ether (30 ml). To this was added 4N HC1 in dioxane (10 ml) and stirred for 2 hr. RPHPLC showed complete reaction. The reaction mixture was concentrated by half, diethyl ether (100mL) was added, and the white solid (1.5 g, 70% yield) filtered and dried under vacuum. ^{1}H NMR was consistent with the desired product ESMS m/z $C_{23}H_{24}N_2O_8S$ = 489 $[M+H]^+$. HRMS calculated for $C_{23}H_{24}N_2O_8S$: 489.1332 $[M+H]^+$, found: 489.1298.

[859] **Example 22. Preparation of 4-[[4-[3-(1,3-dihydro-l-oxo-2H-isoindol-2-yl)propoxy]phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide**



[860] **Part A.** To a solution of 4-[(4-fluorophenyl)-sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (5.2 g, 15 mmol, as prepared in **Example 1, Part C**) in dimethyl sulfoxide (40 ml) at ambient temperature was added N-(3-hydroxypropyl)phthalide (3 g, 15 mmol, prepared according to *J.Med.Chem.*, 146-157 (1996)), followed by cessium carbonate (12 g, 45 mmol). After 15 hr at 80°C, HPLC indicated complete reaction. The reaction mixture was quenched with water (60 ml). The cloudy mixture was extracted with ethyl acetate (2x100 ml). The organic layers were combined, washed with brine (1x200 ml), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a tan, viscous oil that crystallized from methanol (7 g, 720). ESMS m/z = 516 $[M+H]^+$, NMR was consistent with desired product. This material was used without further purification.

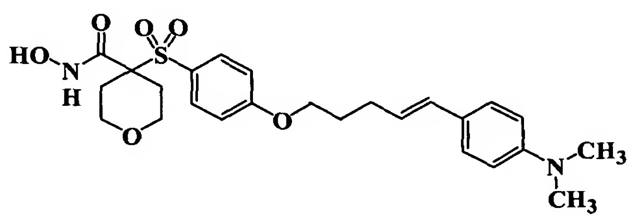
[861] **Part B.** The product from **Part A** (3 g, 6 mmol) was dissolved in methylene chloride (300 ml) and trifluoroacetic acid (6 ml). After 12 hr of stirring, the mixture was concentrated *in vacuo* and the residue was triturated with diethyl ether to form a solid which was collected and dried to afford the carboxylic acid as a beige solid (3 g, 91%). ESMS m/z = 474 $[M+H]^+$. This material was used without further purification.

[862] **Part C.** To a solution of the product from **Part B** (3 g, 6.2 mmol) in N,N-dimethylformamide (25 ml) was added triethylamine (2 ml, 18 mmol), followed by

tetrahydropyranhydroxylamine (1.2 g, 8 mmol), 1-hydroxybenzotriazole (0.5 g, 3 mmol), and 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 g, 8 mmol). The reaction mixture was heated at 40°C for 0.5 hr. The reaction was monitored by RPHPLC. After completion the mixture was concentrated and the residue was flooded with water. The resulting solid was filtered, and was of sufficient purity to carry on to the next step. Mass spectral data and NMR were consistent with the desired product.

[863] **Part D.** The solid from **Part C** (3 g) was slurried in methanol (1 mL) and diethyl ether (30 ml). To this was added 4N HCl in dioxane (10 ml) and stirred for 2 hr. RPHPLC showed complete reaction. The reaction mixture was concentrated by half, diethyl ether (100 mL) was added, and the white solid (2.5 g, 90% yield) filtered and dried under vacuum. ^{1}H NMR was consistent with the desired product. HRMS calculated for $C_{23}H_{26}N_2O_7S$: 475.1525 $[M+H]^+$, found: 475.1510.

[864] **Example 23. Preparation of 4-[[4-[[4E)-5- [-4-(dimethylamino) phenyl]-4-pentenyl]oxy] phenyl] sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide and 4-[[4-[[4Z)-5-[-4-(dimethyl-amino)phenyl]-4-pentenyl]oxy]phenyl]sulfonyl] tetrahydro-N-hydroxy-2H-pyran-4-carboxamide, monohydrochloride**



[865] **Part A.** To a solution of 4-[(4-fluorophenyl)sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid, 1,1-di-methylethyl ester (10.0 g, 29.0 mmol, as prepared in **Example 1, Part C**) in N,N-dimethylformamide (60 ml) at ambient temperature was added 4-penten-l-ol (3.1 ml, 30.0 mmol), followed immediately by NaH (1.4 g, 34.8 mmol, 60% dispersion in mineral oil). After 1.5 hr, HPLC showed less than 1% of the starting material. The reaction mixture was quenched with water (60 ml). The cloudy mixture was extracted with ethyl acetate (3x-300 ml). The organic layers were combined; washed with 5% potassium hydrogensulfate (1x200 ml), saturated sodium bicarbonate solution (1x-200 ml), water (1x-200 ml), and brine (1x-200 ml); dried over sodium sulfate; filtered;

and concentrated *in vacuo* to give a tan oil. The crude product was partially purified by flash chromatography using 15% ethylacetate/hexanes to provide 11.7 g (98%) of the desired ether product as a clear, colorless oil. ESMS m/z = 433 $[M+Na]^+$. This material was used without further purification.

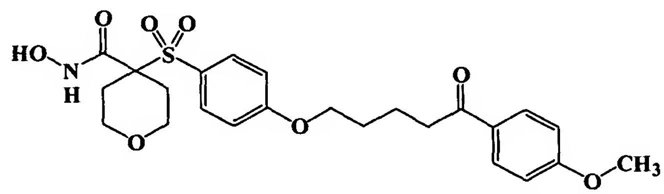
[866] **Part B.** To a solution of the product from **Part A** (2.0 g, 4.9 mmol) in N,N-dimethylformamide (3 ml) was added 4-bromo-N,N-dimethylaniline (1.2g, 5.8 mmol), followed by triethylamine (1.4 ml, 9.8 mmol), tri-ortho-tolylphosphine (34 mg, 0.10 mmol), and palladium(II) acetate (12 mg, 0.05 mmol). The reaction was heated at 100°C for 12 hr. The reaction was cooled and diluted with water (5 ml). The aqueous was extracted with ethyl acetate (3x15 ml). The organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a black oil (3.2 g). The black crude product was partially purified by flash chromatography using 5% ethyl acetate/hexanes to provide 1.2 g of the olefinic product as a tan oil (45% yield, trans:cis, 3:1). ESMS m/z = 552 $[M+Na]^+$. This material was used without further purification.

[867] **Part C.** The product from **Part B** (1.2 g, 2.3 mmol) was dissolved in methylene chloride (4 ml) and trifluoroacetic acid (4 ml). After 1 hr of stirring, the mixture was concentrated and the residue was triturated with diethyl ether to form a solid which was collected and dried to afford the carboxylic acid-TFA salt as a beige solid (0.73 g, 510). ESMS m/z = 474 $[M+H]^+$. This material was used without further purification.

[868] **Part D.** To a solution of the product from **Part C** (0.73 g, 1.2 mmol) in N,N-dimethylformamide (4 ml) was added triethylamine (0.9 ml, 6.2 mmol), followed by tetrahydropyranhydroxylamine (0.28 g, 2.4 mmol), 1-hydroxybenzotriazole (0.19 g, 1.4 mmol), and 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (0.32 g, 1.8 mmol). The reaction mixture was heated at 40°C for 24 hr. The mixture was concentrated and the residue was purified via reverse phase chromatography (C_{18}, acetonitrile/water/TFA). Fractions (10 ml) were collected to separate the isomers. While analyzing, the aqueous TFA mixtures de-protected the product affording the hydroxamic acid final products. 4-[[4-[[4E)-5-[-4-(dimethylamino) phenyl]-4-pentenyl] oxy]phenyl]sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide, (98% trans isomer by HPLC, 0.12 g, 17% yield). HRMS calculated for $C_{23}H_{28}N_2O_8S$: 489.2059 $[M+H]^+$, found: 489.2067. ^1H NMR confirmed trans isomerization (Job = 15.9 Hz). 4-[[4-[[4Z)-5-[-4-(dimethyl-amino)phenyl]-4-pentenyl]oxy]phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-

pyran-4-carboxamide, monohydrochloride, (79% cis/17% trans by HPLC, 15 mg tan solid, 2% yield). HRMS calculated for $C_{25}H_{32}N_2O_6S$: 489.2059 $[M+H]^+$, found: 489.2067.

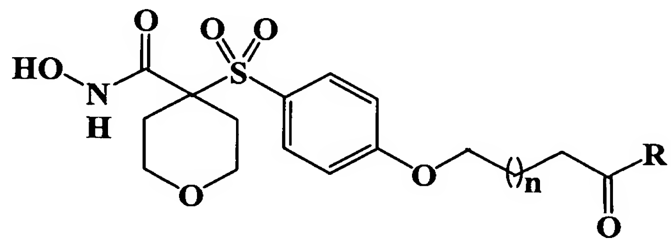
[869] **Example 24. Preparation of tetrahydro-N-hydroxy-4-[[4-[[5(4-methoxyphenyl)-5-oxopentyl]oxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide**



[870] **Part A.** To a mixture of magnesium turnings (344 mg, 14.18 mmol) etched with iodine in anhydrous tetrahydrofuran (4 mL) at reflux was added 4-bromoanisole (1.2 mL, 9.45 mmol) dropwise over 10 min. The reaction mixture was heated at reflux for 45 min, and then cooled to ambient temperature. The prepared grignard reagent was added to a mixture of tetrahydro-4-[[4-[[5-(methoxymethylamino)-5-oxopentyl]oxy]phenyl]sulfonyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-pyran-4-carboxamide (1.0 g, 1.9 mmol, as prepared in **Example 7**) in anhydrous tetrahydrofuran (10 mL) at 0°C. The reaction mixture was warmed to ambient temperature and left stirring overnight. The reaction was quenched with saturated ammonium chloride, and then partitioned between ethyl acetate and water. The layers were separated, and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography using 50-100% ethyl acetate/hexanes to afford 320 mg (29%) of the desired ketone as a white powder. ESMS m/z = 593 $[M+NH_4]^+$. HRMS calculated for $C_{29}H_{37}NO_9S$: 593.2533 $[M+NH_4]^+$, found: 593.2555.

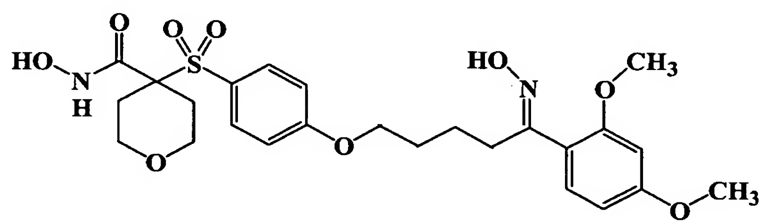
[871] **Part B.** The product from **Part A** (300 mg, 0.52 mmol) was dissolved in 4N HCl in dioxane (3 mL) and methanol (300 uL). After 10 min at ambient temperature, the reaction mixture was poured into hexanes (75 mL), and the product precipitated out as an oil. The solvent was decanted and additional hexanes was added. The resulting solid was triturated with diethyl ether, and the title compound was obtained as an off-white solid. ESMS m/z = 492 $[M+H]^+$. HRMS calculated for $C_{24}H_{29}NO_8S$: 492.1692 $[M+H]^+$, found: 492.1713.

[872] Additional compounds can be prepared by one skilled in the art using similar methods with either the t-butyl ester, THP protected hydroxamate, or resin bound hydroxamate of the weinreb amide. Examples of such compounds include those having a structure corresponding to generic formula EX-I.



EX-I

[873] **Example 25. Preparation of tetrahydro-N-hydroxy-4-[[4-[[5-(hydroxyimino)-5-(4-methoxyphenyl)pentyl]oxy]phenyl]-sulfonyl]-2H-pyran-4-carboxamide.**



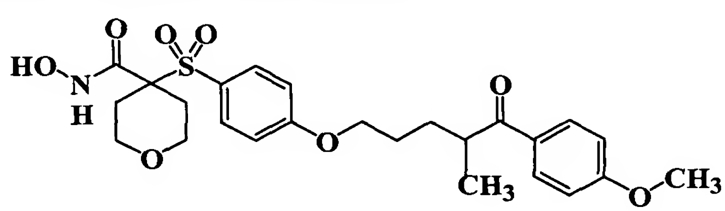
[874] **Part A.** To a mixture of magnesium turnings (1.2 g, 49.4 mmol) etched with iodine in anhydrous tetrahydrofuran (4 mL) at reflux was added 1-bromo-2,4-dimethyoxybenzene (6.0 mL, 41.7 mmol) dropwise over 10 min. The reaction mixture was heated at reflux for 30 min, and then cooled to ambient temperature. The prepared grignard reagent was added to a mixture of tetrahydro-4-[[4-[3-(methoxymethyl-amino)-3-oxopropoxy]phenyl]sulfonyl]-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (1.0 g, 1.9 mmol, prepared as in **Example 7**) in anhydrous THF (10 mL) at 0°C. The reaction mixture was warmed to ambient temperature, and, after 2 hr, was quenched with saturated ammonium chloride, and then partitioned between ethyl acetate and water. The layers were separated, and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was covered with diethylether. The resulting green solid was triturated with diethyl ether. The final solid was collected to

afford 2.2 g (94%) of the desired ketone as a pale green powder. ESMS m/z = 585 $[M+Na]^+$. HRMS calculated for $C_{29}H_{38}NO_9S$: 563 .2315 $[M+H]^+$, found: 563.2319.

[875] **Part B.** The product from **Part A** (2.2 g, 3.91 mmol) was taken up in neat trifluoroacetic acid (6 mL). After 2 hr, the trifluoroacetic acid was removed *in vacuo* at 50°C to give the free acid as a purple oil. ESMS m/z = 507 $[M+H]^+$. To a solution of this material in anhydrous N,N-dimethylformamide (20 mL) was added 1-hydroxybenzotriazole (670 mg, 4.96 mmol), triethylamine (1.8 mL, 12.91 mmol), tetrahydropyranhydroxylamine (1.48 g, 12.63 mmol), and 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (1.13 g, 5.89 mmol). After 16 hr, the reaction mixture was concentrated *in vacuo* at 60°C. The crude material was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was washed with brine (2X), dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield a yellow oil. Purification by flash chromatography using 80% ethyl acetate/hexanes afforded a mixture of THP hydroxamate/THP oxime (78%) and THP hydroxamate ketone (12%). ESMS m/z = 621 $[M+H]^+$ and ESMS m/z = 628 $[M+H]^+$ respectively. These products were not separated, and instead were carried forward as a mixture.

[876] **Part C.** The product from **Part B** (540 mg, 0.77 mmol) was dissolved in 4N HC1 in dioxane (5 mL) and methanol (500 uL). After 2 hr at ambient temperature the reaction mixture was poured into rapidly stirring diethyl ether. A pale pinkish/purple solid was collected and purified by reverse phase HPLC. The title compound was obtained as a white solid. ESMS m/z = 537 $[M+H]^+$. HRMS calculated for $C_{25}H_{32}N_2O_9S$: 537.1907 $[M+H]^+$, found: 537.1921.

[877] **Example 26. Preparation of tetrahydro-N-hydroxy-4-[[4-[[5-(4-methyloxyphenyl)-4-methyl-5-oxopentyl] oxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide**

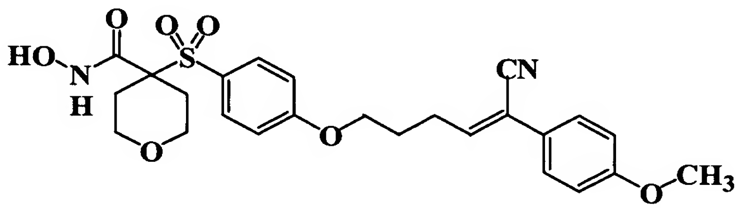


[878] **Part A.** To a solution of tetrahydro-4-[[4-[[5-(4methoxyphenyl)-5-oxopentyl]oxy]phenyl]sulfonyl]-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (532 mg, 1.0 mmol, prepared as in **Example 24**) and iodomethane (623 mg, 4.4 mmol) in 5 ml N,N-dimethylformamide was added sodium hydride (125 mg, 3.1 mmol, 60% dispersion in mineral oil). The reaction was stirred 40 min then quenched with 1N HCl_{aq}. The reaction mixture was partitioned between ethyl acetate and 5% aqueous potassium hydrogensulfate. The organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a crude oil. Purification by flash chromatography using 40% ethyl acetate/hexanes afforded 370 mg (68% yield) of the desired monomethyl ketoester. ESMS m/z = 547 $[M+H]^+$.

[879] **Part B.** The product from **Part A** (370 mg, 0.68 mmol) was taken up in neat trifluoroacectic acid. After 45 min, HPLC analysis indicated that the reaction was complete. The trifluoroacetic acid was removed *in vacuo*, and the residue chased with acetonitrile (2x10 ml), and then vacuum dried to yield 335 mg of the free acid. ESMS m/z = 491 $[M+H]^+$. To a solution of this material in anhydrous N,N-dimethylformamide (4 mL) was added 1-hydroxybenzotriazole (138 mg, 0.68 mmol) and 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (150 mg, 0.78 mmol), followed by triethylamine (190 uL, 1.36 mmol) and tetrahydropyranhydroxylamine (160 mg, 1.37 mmol). After 16 hr, the reaction mixture was partitioned between ethyl acetate and 5% aqueous potassium hydrogensulfate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to a crude oil. Purification by flash chromatography using 60% ethyl acetate/hexanes as eluant afforded 270 mg (67%) of the desired THP protected hydroxamate. ESMS m/z = 590 $[M+H]^+$.

[880] **Part C.** The product from **Part B** (270 mg, 0.46 mmol) was dissolved in 4N HCl in dioxane (2 mL) and methanol (500 uL). After 15 min at ambient temperature, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield 200 mg (86%) of the title compound. ESMS m/z = 406 $[M+H]^+$. HRMS calculated for $C_{25}H_{31}NO_8S$ 506.1849 $[M+H]^+$, found: 506.1828.

[881] **Example 27. Preparation of 4-[[4-[[(4Z)-5-cyano-5-(4-methoxyphenyl)-4-pentenyl]oxy]phenyl]sulfonyl] tetrahydro-N-hydroxy-2H-pyran-4-carboxamide**

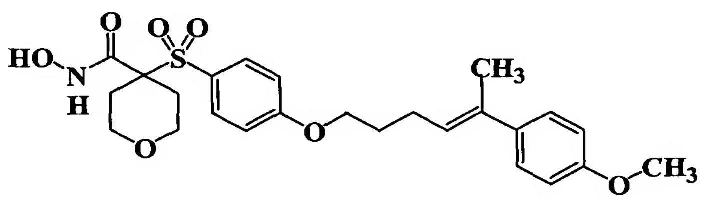


Part A. To a solution of tetrahydro-4-[[4-[[5-(4-methoxyphenyl)-5-oxopentyl]oxy]phenyl]sulfonyl]-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (1.0 g, 1.9 mmol, prepared as in **Example 24**) in 15 ml methylene chloride was added trimethylsilyl cyanide (300 uL, 2.2 mmol) and zinc iodide (660 mg, 2.1 mmol). The reaction was stirred at ambient temperature for 3 hr, and then concentrated *in vacuo*. The residue was partitioned between ethyl acetate and 1 N HCl_{aq}. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 25% ethyl acetate/hexanes to afford 950 mg (81%) of the silylated cyanohydrin. This material was taken up in trifluoroacetic acid (15 mL). The dark red solution showed various peaks by HPLC analysis over the first 40 min. After 1 hr, HPLC analysis indicated 1 new peak at 93%. The reaction mixture was concentrated *in vacuo* and chased with acetonitrile (2x10 ml). The crude solid was dissolved in methanol and added to 40 ml diethyl ether. The resulting white solid was filtered and dried to yield 630 mg of the free acid/cyano olefin. ESMS m/z = 486 $[M+H]^+$.

[882] **Part B.** To a solution of the product from **Part A** (630 mg, 1.3 mmol) in anhydrous N,N-dimethylformamide (15 mL) was added 1-hydroxybenzotriazole (285 mg, 2.1 mmol) and 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (285 mg, 1.5 mmol), followed by N-methylmorpholine (545 uL, 5.0 mmol) and tetrahydropyranhydroxylamine (456 mg, 3.9 mmol). After 20 hr, the reaction mixture was concentrated *in vacuo*, and then partitioned between ethyl acetate and 5% aqueous potassium hydrogensulfate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash chromatography using 80% ethyl acetate/hexanes to afford 530 mg (70%) of the desired THP protected hydroxamate. ESMS m/z = 585 $[M+H]^+$.

[883] **Part C.** The product from **Part B** (530 mg, 0.91 mmol) was dissolved in 4N HC1 in dioxane (5 mL) and methanol (1 mL). After 15 min at ambient temperature, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield 360 mg of the desired hydroxamate. Purification by reverse phase HPLC afforded 270 mg (59%) of the title compound. ESMS m/z = 504 $[M+H]^+$. HRMS calculated for $C_{25}H_{28}N_2O_7S$: 501 . 1695 $[M+H]^+$, found: 501. 1689.

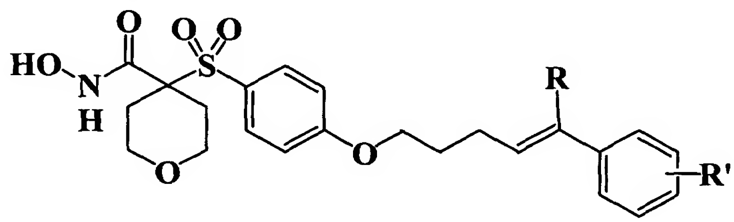
[884] **Example 28. Preparation of tetrahydro-N-hydroxy-4-[[4[[(4E)-5-(4-methoxyphenyl)-4-hexenyl]oxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide**



[885] **Part A.** To a cooled (0°C) solution of 4-[(4-{[5-(4-methoxyphenyl)-5-oxopentyl]oxy}phenylsulfonyl]-N-(tetrahydro-2H-pyran-2-yloxy)tetrahydro-2H-pyran-4-carboxamide (0.2 g, 0.4 mmol, as prepared in **Example 24**) in tetrahydrofuran (2 ml) was added a 3.0 M solution of methylmagnesium bromide (1.2 ml, 3.6 mmol). The ice bath was removed, and the reaction stirred for 2 hr at room temperature. HPLC showed less than 1% of the ketone starting material. The reaction mixture was diluted with ethyl acetate and washed with saturated ammonium chloride solution, water, and brine. After drying over sodium sulfate and filtering, the organic layer was concentrated *in vacuo* to afford 0.25 g (100%) of a tan oil. ESMS m/z = 614 $[M+Na]^+$. This material was used without further purification.

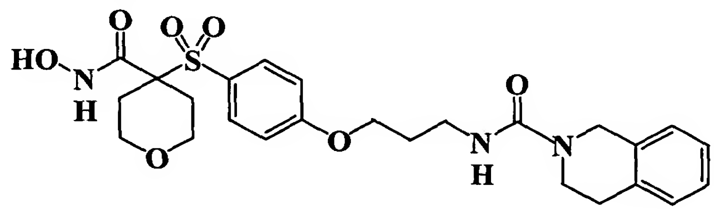
[886] **Part B.** To the product from **Part A** (0.24 g, 0.4 mmol) was added methanol (0.5 ml) and 4 N HCl in dioxane (4.0 ml). After stirring 2 hr, HPLC showed no remaining starting material. Diethyl ether was added to form a solid but a gummy residue developed. The mixture was concentrated and the oily residue was purified via reverse phase HPLC (C_{18}, acetonitrile/water/TFA) to afford 0.11 g (55%) of the desired product as a tan oil. ^{1}H NMR (N.O.E) confirmed the isomerized mixture as 70% trans:30% cis. HRMS calculated for $C_{25}H_{31}NO_7S$: 490.1899 [M+H], found: 490.1898.

[887] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-J.



EX-J

[888] **Example 29 Preparation of 3,4-dihydro-N-[3-[4-[[tetrahydro-4-[(hydroxyamino)carbonyl]-2H-pyran-4-yl]sulfonyl]-phenoxy] propyl]-2-(1H)-isoquinolinecarboxamide**



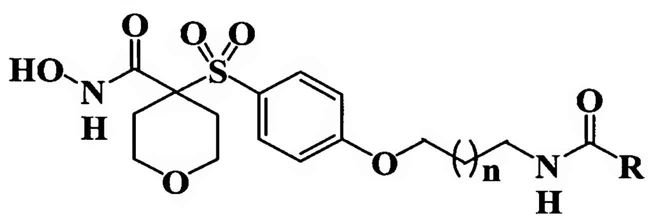
[889] **Part A.** To a solution of 4-[[4-(3-aminopropoxy)-phenyl]sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid 1,1-dimethylethyl ester, monohydrochloride (467 mg, 1.07 mmol, prepared in **Example 1**) in anhydrous chloroform (3 mL) at ambient temperature was added triethylamine (170 uL, 1.22 mmol) and 1,1'-carbonyldiimidazole (180 mg, 1.11 mmol). After 1 hr at 50°C, 1,2,3,4-tetrahydroisoquinoline (162 mg, 1.22 mmol) was added neat. After an additional 2 hr at 50°C, HPLC indicated complete reaction. The reaction mixture was partitioned between ethyl acetate and 5% aqueous potassium hydrogen sulfate. The organic layer was washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a yellow oil. ESMS m/z = 559 $[M+H]^+$. This material was used without further purification.

[890] **Part B.** The product from **Part A** was taken up in neat trifluoroacetic acid (3 mL). After 13 hr, the trifluoroacetic acid was removed *in vacuo* at 50°C to give the free acid. ESMS m/z = 503 $[M+H]^+$. To a solution of this material in anhydrous N,N-

dimethylformamide (5 mL) was added 1-hyrdoxybenzotriazole (176 mg, 1.30 mmol), triethylamine (500 uL, 3.59 mmol), and tetrahydropyranhydroxylamine (254 mg, 2.17 mmol), followed by 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (310 mg, 1.62 mmol). The reaction mixture was heated at 40°C for 4 hr, and then stirred at ambient temperature overnight. The reaction mixture was concentrated *in vacuo* at 60°C. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The layers were separated, and the organic layer was washed with brine (3X), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography to give 260 mg (40% from the starting amine) of the desired THP protected hydroxamate as a white solid. ESMS m/z = 624 $[M+Na]^+$. HRMS calculated for $C_{30}H_{39}N_3O_8S$: 602 .2536 $[M+H]^+$, found: 602 .2546 .

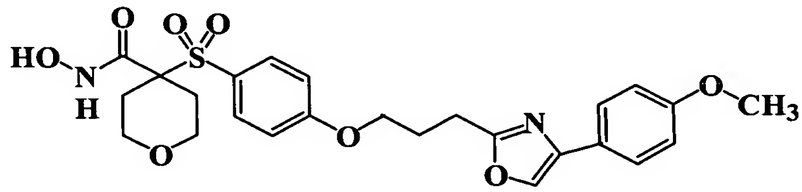
[891] **Part C.** The product from **Part B** (252 mg, 0.42 mmol) was dissolved in 4N HCl in dioxane (5 mL) and methanol (500 uL). After 1 hr at ambient temperature, the reaction mixture was poured into rapidly stirring diethyl ether. A white solid was collected and dried over P205 under vacuum. The title compound was obtained as a white solid. ESMS m/z = 518 $[M+H]^+$. HRMS calculated for $C_{25}H_{31}N_3O_7S$: 518. 1961 $[M+H]^+$, found: 518.1961.

[892] Additional compounds can be prepared by one skilled in the art using similar methods (urea formation also can be achieved by coupling the starting amine with and an isocyanate). Examples of such compounds include those having a structure corresponding to generic formula EX-K.



EX-K

[893] **Example 30. Preparation of tetrahydro-N-hydroxy-4-[[4-[3-[4-(4-methoxyphenyl)-2-oxazolyl]propoxy]phenyl]sulfonyl]-2Hpyran-4-carboxamide**



[894] **Part A.** To a solution of 4-[[4-(3-carboxypropoxy)phenyl]sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (3.2 g, 7.5 mmol, prepared as in **Example 7**) in acetone (15 mL) was added 2-bromo-4-methoxyacetophenone (1.72 g, 7.5 mmol) and potassium carbonate (1.04 g, 7.5 mmol). The reaction mixture was stirred at ambient temperature for 3 hr. The reaction mixture was filtered, and the cake washed with acetone. The acetone solution was concentrated *in vacuo*. Purification by flash column chromatography using ethyl acetate/hexanes provided 3.68 g (85%) of the substituted ester as a white solid. ESMS m/z = 599 $[M+Na]^+$.

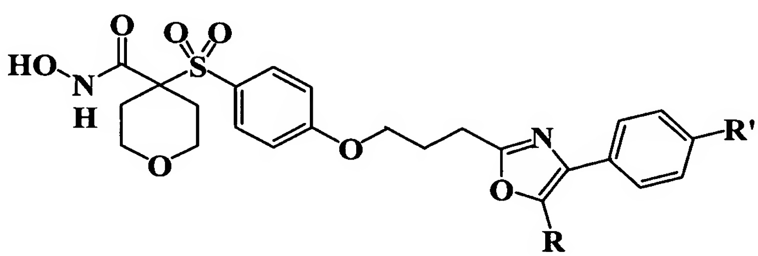
[895] **Part B.** The product from **Part A** (3.6 g, 6.25 mmol) was refluxed in acetic acid (12 mL) with ammonium acetate (2.41 g, 31.25 mmol) for 24 hr. The reaction was diluted with ethyl acetate (50 mL) and washed 2 times with water (25 mL) and filtered. The ethyl acetate filtrate was extracted with a 10% aqueous NaOH (50 mL). The basic solution was then acidified to a pH of 1, and then extracted with ethyl acetate (25 mL). The organic solution was then washed with water (25 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 1.5 g (48%) of the carboxylic acid of the oxazole as a brown solid. ESMS m/z = 502 $[M+H]^+$.

[896] **Part C.** In dry equipment under nitrogen, the carboxylic acid from **Part B** (1.3 g, 2.59 mmol) was dissolved in dry N,N-dimethylformamide (5 mL), and the remaining reagents were added to the solution in the following order: 1-hydroxybenzotriazole (490 mg, 3.63 mmol), triethylamine (0.43 mL, 3.11 mmol), tetrahydropyranhydroxylamine (364 mg, 3.11 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (746 mg, 3.89 mmol). After 12 hr at 40°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated sodium bicarbonate solution, and brine, dried over sodium sulfate, filtered, and

concentrated *in vacuo*. Purification by flash column chromatography using ethyl acetate/hexanes provided 0.70 g (450) of the THP hydroxamate as a white foam. ESMS m/z = 601 $[M+H]^+$.

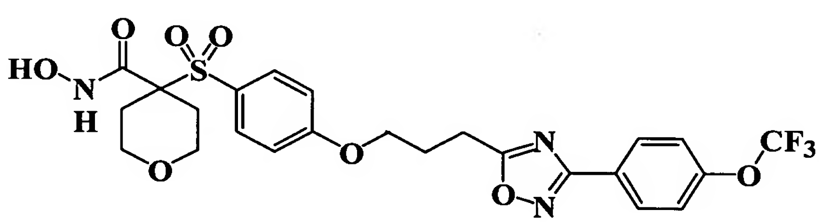
[897] **Part D.** To a solution of the product from **Part C** (0.6 g, 1.0 mmol) in 1,4-dioxane (1.0 mL) was added 4N HCl in dioxane (1.25 mL, 5 mmol) and methanol (0.13 mL). After 1 hr at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Methylene chloride (20 mL) was added, and the solution was stripped to afford 0.29 g (56%) of the title compound as a light pink solid. HRMS calculated for $C_{25}H_{28}N_2O_8S$: 517.1645 $[M+H]^+$, found: 517.1651.

[898] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-L.



EX-L

[899] **Example 31. Preparation of tetrahydro-N-hydroxy-4-[[4-[3-[3[4-(trifluoromethoxy)phenyl]-1,2,4-oxadiazol-5-yl]propoxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide**



[900] **Part A.** In dry equipment under nitrogen, 4-[[4-(3-carboxypropoxy)phenyl]sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (2.57 g, 6.0 mmol, prepared as in **Example 7**) was dissolved in dry N,N-dimethylformamide (12 mL), and the remaining reagents were added to the solution

in the following order: 1-hydroxybenzotriazole hydrate (1.13 g, 8.4 mmol), triethylamine (1.0 mL, 7.2 mmol), 4-(trifluoromethoxy)benzamidoxime (1.58 g, 7.2 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.73 g, 9.0 mmol). After 2 hr at 35°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated sodium bicarbonate solution, and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography using ethyl acetate/hexanes afforded 3.05 g (81%) of the desired product as a clear glass. ESMS m/z = 631 $[M+Na]^+$.

[901] **Part B.** The product from **Part A** (2.9 g, 4.60 mmol) was heated at 90°C in toluene (15 mL) for 30 hr. The reaction was concentrated *in vacuo*. Purification by column chromatography using ethyl acetate/hexanes afforded 2.06 g (73%) of the oxadiazole as a white solid. ESMS m/z = 635 $[M+Na]^+$.

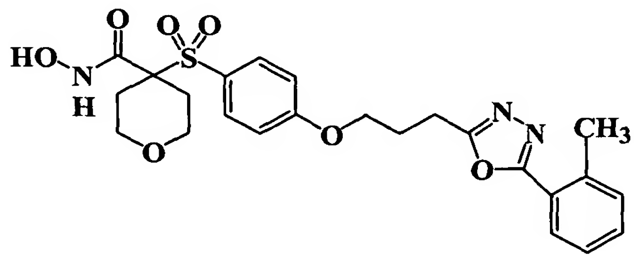
[902] **Part C.** The product from **Part B** (2.0 g, 3.27 mmol) was dissolved in trifluoroacetic acid (8 mL) and stirred at ambient temperature for 2 hr. The reaction was diluted with methylene chloride (10 mL) and concentrated *in vacuo*. Methylene chloride (10 mL) was added to the residue and concentrated *in vacuo* again to provide 1.8 g (99%) of the free acid as an off- white solid. ESMS m/z = 557 $[M+H]^+$.

[903] **Part D.** In dry equipment under nitrogen, the product from **Part C** (1.7 g, 3.06 mmol) was dissolved in dry N,N-dimethylformamide (6 mL), and the remaining reagents were added to the solution in the following order: 1-hydroxybenzotriazole hydrate (578 mg, 4.28 mmol), triethylamine (0.51 mL, 3.67 mmol), tetrahydropyranhydroxylamine (429 mg, 3.67 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (879 mg, 4.59 mmol). After 90 min at 40°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated sodium bicarbonate solution, and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography using ethyl acetate/hexanes provided 1.9 g (95%) of the THP hydroxamate as a white foam. ESMS m/z = 678 $[M+Na]^+$.

[904] **Part E.** To a solution of the product from **Part D** (1.8 g, 2.75 mmol) in 1,4-dioxane (1.0 mL) was added 4N HCl in dioxane (3.5 mL, 13.7 mmol) and methanol (0.35 mL). After 2 hr at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over sodium sulfate, filtered, and concentrated *in vacuo*.

Reverse phase chromatography provided 1.12 g (71%) of the title compound as a white solid. HRMS calculated for $C_{24}H_{24}N_3O_8S_1F_3$: 572.1314 $[M+H]^+$, found: 572.1290.

[905] **Example 32. Preparation of tetrahydro-N-hydroxy-4-[[4-[3-[5-(2-methylphenyl)-1,3,4-oxadiazol-2-yl]propoxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide**



[906] **Part A.** In dry equipment under nitrogen, 4-[[4-(3-carboxypropoxy)phenyl]sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (2.14 g, 5.0 mmol, prepared as in **Example 7**) was dissolved in dry N,N-dimethylformamide (10 mL), and the remaining reagents were added to the solution in the following order: 1-hydroxybenzotriazole hydrate (945 mg, 7.0 mmol), triethylamine (0.84 mL, 6.0 mmol), o-toluic hydrazide (901 mg, 6.0 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.44 g, 7.5 mmol). After 2 hr at 35°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate; washed with water, saturated sodium bicarbonate solution, and brine; dried over sodium sulfate; filtered; and concentrated *in vacuo*. Purification by flash column chromatography using ethyl acetate/hexanes provided 2.32 g (83%) of the desired product as a white foam. ESMS m/z = 583 $[M+Na]^+$.

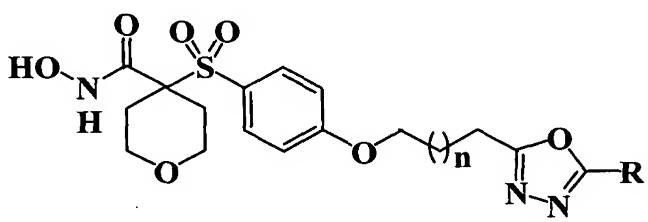
[907] **Part B.** The product from **Part A** (2.1 g, 3.75 mmol) was heated to reflux in toluene (25 mL) with p-toluenesulfonic acid (100 mg) for 4 hr. The reaction was concentrated *in vacuo*. Recrystalization from hot methanol provided 1.6 g (88%) of the free acid of the oxadiazole as a white solid. ESMS m/z = 487 $[M+Na]^+$.

[908] **Part C.** In dry equipment under nitrogen, the product from **Part B** (1.5 g, 3.09 mmol) was dissolved in dry N,N-dimethylformamide (6 mL), and the remaining reagents were added to the solution in the following order: 1-hydroxybenzotriazole hydrate (578 mg, 4.28 mmol), triethylamine (0.51 mL, 3.67 mmol),

tetrahydropyranhydroxylamine (429 mg, 3.67 mmol), and 1-(3 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (879 mg, 4.59 mmol). After 6 hr at 40°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate; washed with water, saturated sodium bicarbonate solution, and brine; dried over sodium sulfate; filtered; and concentrated *in vacuo*. Purification by flash column chromatography using ethyl acetate/hexanes provided 1.53 g (85%) of the THP hydroxamate as a white foam. ESMS m/z = 608 $[M+Na]^+$.

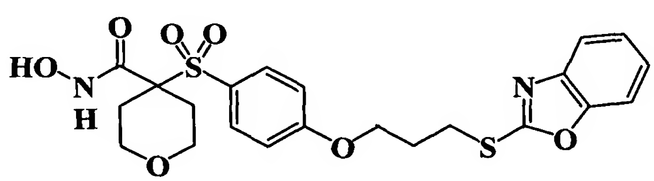
[909] **Part D.** To a solution of the product from **Part C** (1.4 g, 2.39 mmol) in 1,4-dioxane (1.0 mL) was added 4N HCl in dioxane (6 mL, 23.9 mmol) and methanol (0.6 mL). After 2 hr at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Reverse phase chromatography provided 1.02 g (85%) of the title compound as a white solid. HRMS calculated for $C_{24}H_{27}N_3O_7S_1$: 502.1648 $[M+H]^+$, found: 502.1652.

[910] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-M..



EX-M

[911] **Example 33. Preparation of 4-[[4-[3-(2-benzoxazolylthio)propoxy]phenyl]sulfonyl]tetrahydro-N-N-hydroxy-2H-pyran-4-carboxamide.**

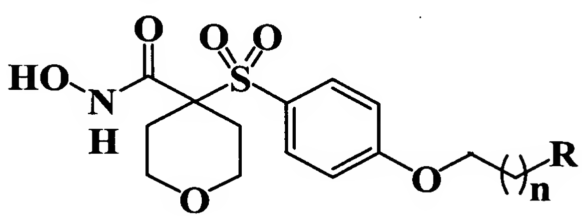


[912] **Part A.** To a solution of 2-mercaptobenzoxazole (290 mg, 1.92 mmol) in N,N-dimethylformamide (5 mL) at 0°C was added NaH (128 mg, 1.92 mmol, 60%

dispersion in mineral oil). After 30 min, tetrahydro-4-[[4-[3-[(methylsulfonyl-)oxy]propoxy]phenyl]sulfonyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-pyran-4-carboxamide (1.0 g, 1.92 mmol, prepared as in **Example 29)** was added, and the solution was stirred for 2 hr at 65°C. The solution was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 510 mg (46%) of the thiobenzoxazole as a crude dark oil. ESMS m/z = 577 $[M+H]^+$.

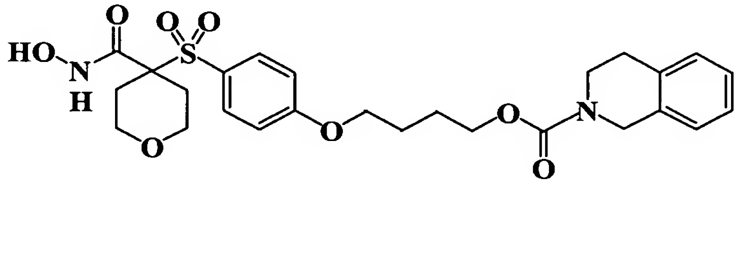
[913] **Part B.** To a solution of the crude thiobenzoxazole of **Part A** (505 mg, 0.88 mmol) in 1,4-dioxane (5 mL) was added 4 N HCl in dioxane (5 mL), and was stirred for 2 hr. Purification by reverse phase HPLC (C_{18}, acetonitrile/water) provided 257 mg (60%) of the title compound as a white solid. ESMS m/z = 493 $[M+H]^+$. HRMS calculated for $C_{22}H_{24}N_2O_7S_2$: 493.1103, found 493.1122. Analytical calculation for $C_{22}H_{24}N_2O_7S_2 \cdot 0.3H_2O$: C, 53.06; H, 4.98; N, 5.63; S, 12.88. Found: C, 53.08; H, 5.03; N, 5.62; S 12.69.

[914] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-N.



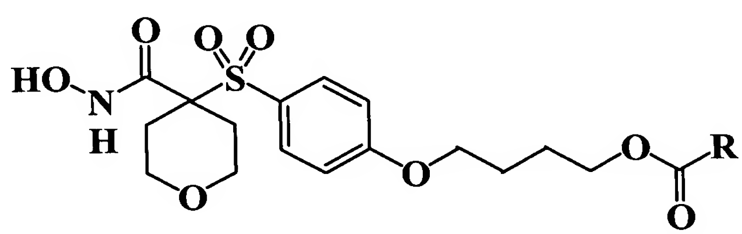
EX-N

[915] **Example 34. Preparation of 4-[[4-[[tetrehydro-4-[(hydroxyamino)carbonyl]-2H-pyran-4-yl]sulfonyl]cyclohexyl]oxy]butyl ester 3,4-dihydro-2(1H)-isoquinolinecarboxylic acid**



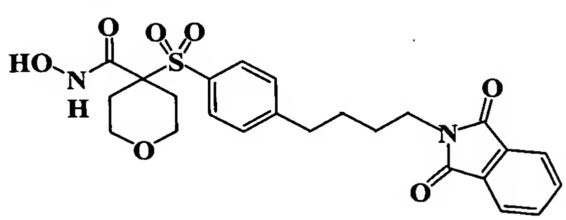
[916] **Part A.** To a solution of tetrahydro-4-[[4-[4-[(methyl-sulfonyl)oxy]butoxy]phenyl] sulfonyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-pyran-4-carboxamide (200 mg, 0.37 mmol, synthesized in a fashion similar to **Example 29)** in anhydrous N,N-dimethylformamide (2 mL) was added to 1,2,3,4-tetrahydroisoquinoline (0.24 mL, 1.9 mmol) and cesium carbonate (0.62 g, 1.9 mmol). The reaction mixture was stirred at ambient temperature overnight. The crude reaction mix was poured onto a 20 mL ChemElut tube (celite) prewetted with 15 mL of water, and eluted with 1:1 ethyl acetate:methylene chloride. Purification by reverse phase HPLC (C18, acetonitrile/water), followed by treatment with 2 mL of 4N HCl in dioxane, provided 12.2 mg (6.2 %) of the desired product as an amorphous solid after lyophilization. ESMS m/z = 531 [M+H]'. HRMS calculated for $C_{26}H_{33}N_2O_8S$: 533.1958 $[M+H]^+$, found: 533.1943.

[917] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-O.



EX-O

[918] **Example 35. Preparation of 4-[[4-[4-(1,3-dihydro-l,3-dioxo-2H-isoindol-2-yl)butyl]phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide**



[919] **Part A.** A solution of 4-bromobenzenethiol (28.5 g, 151 mmol) in N,N-dimethylformamide (250 mL) was purged with nitrogen for 10 min and then potassium carbonate (22.9 g, 166 mmol) was added. After purging for another 10 min with nitrogen, t-butyl bromoacetate (24.5 g, 166 mmol) was added, and the reaction was stirred at

ambient temperature for 1 hr. The reaction was chilled to 0°C and diluted with water (250 mL). The slurry was extracted with ethyl acetate. The organic layer was washed with water, saturated sodium bicarbonate solution, and brine; dried over sodium sulfate; filtered; and concentrated *in vacuo* to provide 49.8g (100%) of the sulfide as a light yellow oil. ESMS m/z = 3 2 0 $[M+NH4]^+$.

[920] **Part B.** To a solution of the product from **Part A** (45.67 g, 151 mmol) in tetrahydrofuran (300 mL) was added water (75 mL) and Oxone™ (278.5 g, 453 mmol) at 20°C. An exotherm to 43°C was observed. After 3 hr, the reaction was filtered, and the cake was washed well with tetrahydrofuran. The filtrate was concentrated *in vacuo* to 1 third the volume. The residue was taken up in ethyl acetate, washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 51.0 g (100%) of the sulfone as a crystalline solid. ESMS m/z = 335 $[M+H]^+$.

[921] **Part C.** To a solution of the product from **Part B** (23.45 g, 16 mmol) in N,N-dimethylformamide (140 mL) was added potassium carbonate (19.3 g, 140 mmol), bis-(2-bromoethyl)ether (9.1 mL, 70 mmol), and 18-Crown-6 (1 g). The slurry was stirred at 60°C. After 16 hr, the reaction was filtered, and the filtrate was concentrated *in vacuo.* The residue was taken up in ethyl acetate, washed with water (3X) and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The product was recrystallized from methanol to provide 19.79 g (70%) of the desired compound as a white solid. (ESMS m/z = 405 $[M+H]^+$.

[922] **Part D.** To a solution of N-(3-buten-l-yl)phthalimide (1.2 g, 5.97 mmol) in anhydrous tetrahydrofuran (3 mL) at 0°C was added 0.5 M 9-borobicyclononane in tetrahydrofuran (11.9 mL, 5.97 mmol) dropwise. The resultant solution was stirred with cooling for 10 min, and then the ice bath was removed. After 18 hr, the product from **Part C** (1 g, 2.98 mmol), tetrakis(triphenyl-phosphine)palladium(0) (172 mg, 0.15 mmol) and 2 M sodium carbonate (3 mL, 6 mmol) were added, and the reaction mixture was heated to 65°C for 2 hr. After cooling to ambient temperature, the solution was concentrated *in vacuo*. The residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The layers were separated, and the organic layer was washed with water (50 mL) and brine (50 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography using 25-50% ethyl acetate/hexanes yielded 1.21 g of the

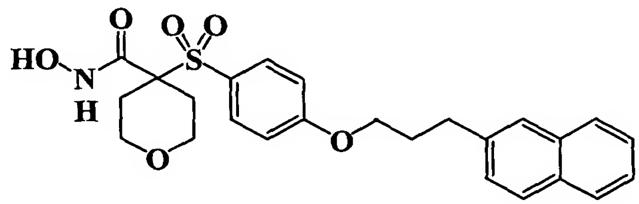
desired compound as an off-white solid. HRMS calculated for $C_{28}H_{37}N_2O_7S$: 545.2321 $[M+H]^+$, found: 545.2311.

[923] **Part E.** To a solution of the product from **Part D** (1.16 g, 2.2 mmol) in anhydrous methylene chloride (20 mL) at ambient temperature was added trifluoroacetic acid (20 mL). The solution was stirred for 2 hr, and then concentrated *in vacuo*. The resulting residue was dissolved in methanol (50 mL) and concentrated *in vacuo*, and subsequently dissolved in methylene chloride (50 mL) and concentrated *in vacuo*. Trituration with hexanes yielded 0.98 g of the carboxylic acid as an off-white solid. HRMS calculated for $C_{28}H_{37}N_2O_7S$: 489.1695 $[M+NH_4]$, found: 489.1702.

[924] **Part F.** To a solution of the product from **Part E** (0.95 g, 2.01 mmol) in a mixture of methylene chloride (4 mL) and N,N-dimethylformamide (4 mL) was added triethylamine (0.28 mL, 2.01 mmol), 1-hydroxybenzotriazole (0.407 g, 3.015 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.538 g, 2.814 mmol). After 10 min, additional triethylamine (0.56 mL, 4.02 mmol) and tetrahydropyranhydroxylamine (0.706 g, 6.03 mmol) were added. The solution was warmed to 38°C and stirred for 20 hr. The mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with 1 M HC1 (50 mL), water, brine. After drying over magnesium sulfate, the organic layer was concentrated to give 1.31 g of an off white solid. Purification by flash column chromatography using 25-50% ethyl acetate/hexanes yielded 1.05 g of the pure product as a white solid. HRMS calculated for $C_{29}H_{34}N_2O_8SNa$: 593.1934 [M+Na], found: 593.1967.

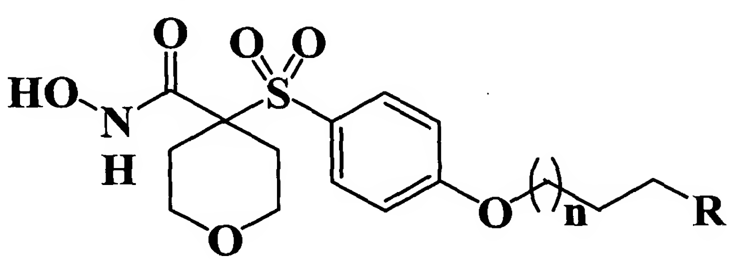
[925] **Part G.** To a solution of the product from **Part F** above (0.255 g, 0.446 mmol) in a mixture of methanol (3 mL) and dioxane (3 mL) was added 4 N HCl in dioxane (3 mL). The mixture was stirred at ambient temperature for 10 min, and then concentrated *in vacuo*. Trituration with diethyl ether/hexanes yielded 224 mg of the title compound as a white solid. HRMS calculated for $C_{24}H_{27}N_2O_7S$: 487.1539 [M+H], found: 487.1559.

[926] **Example 36. Preparation of 2H-pyran-4-carboxamide, tetrahydro-N-hydroxy-4[[4-[3-(2-naphthalenyl)propoxy]-phenyl]sulfonyl]**



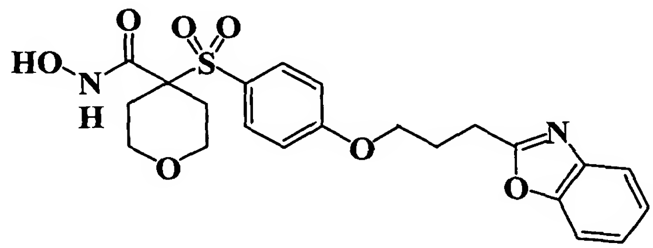
[927] To a solution of (tetrahydro-4-[[4-(2propenyloxy)phenyl]sulfonyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-pyran-4-carboxamide (200 mg, 0.47 mmol, prepared as in **Example 35**) in tetrahydrofuran (1 mL) was added 0.5 M 9-borobicyclononane (0.94 mL, 0.47 mmol). The solution was stirred at ambient temperature for 16 hr. To this solution was added 2 M sodium carbonate (0.5 mL, 1 mmol), 2-bromonaphthalenylene (108 mg, 0.52 mmol), and tetrakis(triphenylphosphine)palladium(0) (54 mg, 0.047 mmol). The mixture was heated to 65°C for 4 hr, and then cooled to ambient temperature. Saturated ammonium chloride solution (3 mL) was added to the reaction mixture. The resulting mixture was filtered through a small column of celite. The column was washed with ethyl acetate (35 mL). The eluant was concentrated *in vacuo*, and the residue was dissolved in methanol (3 mL), dioxane (3 mL), and 4 N HC1 in dioxane. After 10 min, the solution was concentrated *in vacuo*, and the residue purified by preparative reverse phase HPLC (10-90% acetonitrile/0.05% TFA in water) yielding 20 mg of the title compound as a white solid. HRMS calculated for $C_{25}H_{28}NO_6S$: 470.1670 [M+H], found: 470.1614.

[928] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-P.



EX-P.

[929] **Example 37. Preparation of 4-[[4-[3-(2-benzoxazolyl)propoxy]phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide**



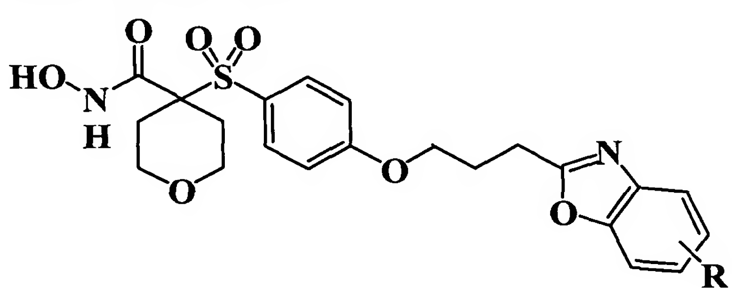
[930] **Part A.** To a solution of 4-[[4-(3-carboxypropoxy)phenyl]sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (3.0 g, 7.0 mmol) in N,N-dimethylformamide (14 mL) was added 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (1.88 g, 9.8 mmol) and 1-hydroxybenzotriazole (1.32 g, 9.8 mmol). The resulting suspension became a clear amber solution after stirring at 50°C for 1.5 hr. The reaction was then treated with 2-aminophenol (0.76 g, 7.0 mmol), followed by N-methylmorpholine (2.3 mL, 21.0 mmol). The reaction was stirred at 50°C overnight. After 21 hr, the reaction was partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate. The organic layers were combined and washed with saturated sodium bicarbonate solution, water, 1:1 solution of water:brine, and brine; dried over sodium sulfate; filtered; and concentrated *in vacuo.* The resulting oil was purified on silica gel using ethyl acetate/hexanes to afford 2.98 g (82%) of the amide as an amber oil. ESMS m/z = 542 $[M+Na]^+$.

[931] **Part B.** To a suspension of the product from **Part A** the (1.59 g, 3.1 mmol) toluene (50.0 mL) was added p-toluenesulfonic acid (0.12 g, 0.6 mmol), and the resulting mixture heated at reflux under Dean-Stark conditions. After 39 hr, the reaction was concentrated *in vacuo*, and the resulting residue was partitioned between ethyl acetate and 1 M aqueous hydrochloric acid. The organic layer was washed with 1 M aqueous hydrochloric acid, water, and brine; dried over sodium sulfate; filtered; and concentrated *in vacuo* to afford 1.25 g (92%) of the crude carboxylic acid benzoxazole as a tan, white solid. ESMS m/z = 446 $[M+H]^+$.

[932] **Part C.** To a solution of the product from **Part B** (0.98 g, 2.2 mmol) in N,N-dimethylformamide (10.0 mL) was added 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (0.59 g, 3.1 mmol) and 1-hydroxybenzotriazole (0.42 g, 3.1 mmol). The resulting suspension became a clear amber solution after stirring at 50°C for 0.5 hr. The reaction was then treated with tetrahydropyranhydroxylamine (0.36 g, 3.1 mmol), followed by N-methylmorpholine (0.73 mL, 6.6 mmol). The reaction was stirred at 50°C overnight. After 12 hr, the reaction was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The organic layers were combined and washed with saturated sodium bicarbonate solution, water, 1:1 solution of water:brine, and brine; dried over sodium sulfate; filtered; and concentrated *in vacuo*. The resulting oil was purified on silica gel using ethyl acetate/hexanes as eluant to afford 1.2 g (98%) of the THP hydroxamate benzoxazole as an amber oil. ESMS m/z = 545 $[M+H]^+$.

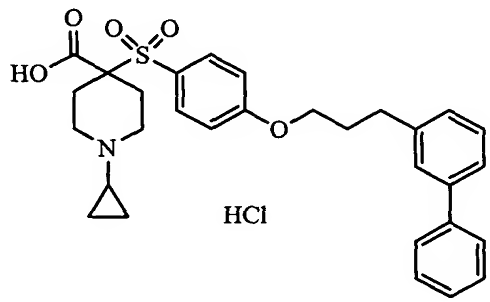
[933] **Part D.** To a solution of the product from **Part C** (0.104 g, 0.19 mmol) in a mixture of methanol (0.3 mL) and dioxane (2 mL) was added 4 N HCl in dioxane (0.5 mL). The mixture was stirred at ambient temperature for 30 min, concentrated in half *in vacuo*, and diluted with diethyl ether. Filtration afforded 17 mg (20%) of the title compound as a tan solid. HRMS calculated for $C_{22}H_{24}N_2O_7S$: 461.1382 [M+H], found: 461.1374.

[934] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-Q.

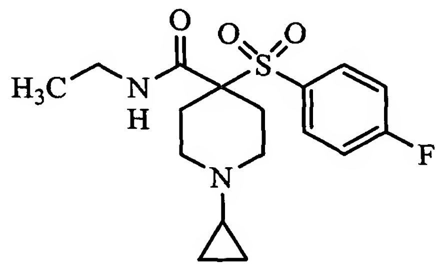


EX-Q.

[935] **Example 38. Preparation of:**

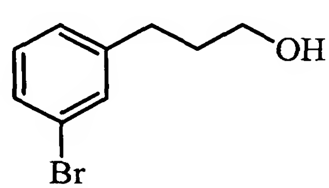


[936] **Part A.** Preparation of:



To a solution of ethyl 4-[(4-fluorophenyl)sulfonyl]piperidine-4-carboxylate hydrochloride (60.0 g, 170 mmol) in methanol (600 mL), were added acetic acid (97 mL, 1.7 mole), [(1-ethoxycyclopropyl)oxy]trimethylsilane (102 mL, 510 mmol) and 4A molecular sieves (55 g) followed by sodium cyanoborohydride (28.8 g, 459 mmol). The solution was stirred at ambient temperature overnight, then refluxed for 6 hr. The reaction mixture was filtered through celite and concentrated to solid/oil mix. Ethyl acetate and saturated sodium bicarbonate were added very carefully. When aqueous layer stayed basic, the layers were separated and the organic layer was washed 3 times with saturated sodium bicarbonate, then with brine and then dried over sodium sulfate. Concentration *in vacuo* and crystallization from ethyl acetate/hexane provided the n-cyclopropyl compound as an off white solid (53.8 g, 88.8%). ESMS $_{m/z}$ = 356 (M+H).

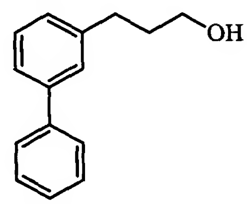
[937] **Part B.** Preparation of:



To a solution of 3-(3-bromophenyl)propionic acid (10.0 g, 43.7 mmol) in anhydrous THF (150 mL) was added 1.0 M BH_3·THF (150 mL, 150 mmol) via addition funnel. After

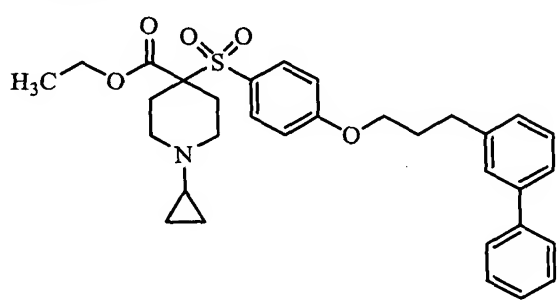
BH_3·THF was added, the reaction was refluxed for 18 hrs. The reaction was quenched with water (100 mL) and 1N HC1 (300 mL). The solution was saturated with sodium chloride and extracted with ethyl acetate. The organic extract was washed with brine and dried over magnesium sulfate. The organic material was purified by chromatography on silica gel eluting with ethyl acetate in hexane to produce 9.39 g (100 %) of the desired alcohol as a colorless oil. NMR ($CDCl_3$) δ 1.82-1.89 (m, 2H), 2.67 (t, 2H) , 3.64 (t, 2H), 7.11 7.15 (m, 1H), 7.29-7.31 (m, 1H), 7.34 (s, 1H).

[938] **Part C.** Preparation of:



In a flask were combined the alcohol from **Part B** (3.43 g, 16.0 mmol), phenyl boronic acid (2.93 g, 24.0 mmol), palladium tetrakistriphenylphosphine (0.92 g, 0.8 mmol), 2M cesium carbonate (24 mL, 48 mmol) and dimethoxyethylether (48 mL). The mixture was stirred vigorously under nitrogen at reflux. After 1.5 hr the reaction was cooled to ambient temperature, diluted with water and extracted with ether 3 times. The combined organic extracts were washed with brine and dried over magnesium sulfate. 2.74 g (81% yield) purified product was obtained as a crystalline solid by chromatography (on silica, ethyl acetate/hexane). NMR ($CDCl_3$) δ 1.91-1.98 (m, 2H) , 2.77 (t, 2H), 3.71 (t, 2H), 7.19 (d, 1H), 7.31-7.38 (m, 2H), 7.41-7.45 (m, 4H), 7.58 (d, 2H).

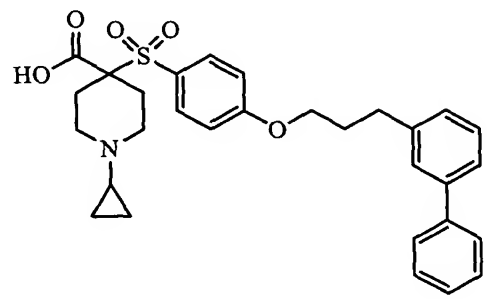
[939] **Part D.** Preparation of:



To a solution of the alcohol from **Part C** (2.7 g, 12.7 mmol) in anhydrous dimethylformamide (12 mL) at 0°C was added 60 % sodium hydride (0.58 g, 14.5 mmol) in portions. After that the reaction was stirred at 0°C for 15 min and then at ambient

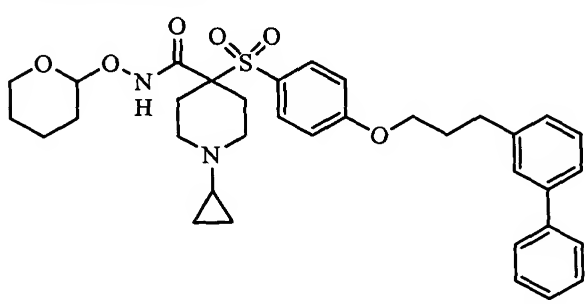
temperature for 15 min. The reaction mixture was cooled to 0°C and the cyclopropyl compound from **Part A** (4.3 g, 12.4 mmol) in anhydrous dimethylformamide (10 mL) was added slowly. Upon completion of addition, ice bath was removed and the reaction stirred at ambient temperature for 1 hr the reaction, then diluted with water and extracted with ethyl acetate 3 times. The combined organic extracts were washed with saturated $NaHC0_3$ and brine and dried over sodium sulfate. After concentration 4.63 g of material was obtained. This material was used without purification.

[940] **Part E.** Preparation of:



The ester of **Part D** (4.61 g, 8.4 mmol) was hydrolyzed in 1:1:0.56 mixture of ethanol:1,4-dioxane:6N NaOH (25.6 mL) at 60°C. The solution was concentrated *in vacuo*, diluted with water and extracted with ether to remove color. Acidification with 1N HCl caused precipitation of the acid which was collected by filtration, washed with water and hexane and dried under high vacuum yielding the acid as an off white solid (3.45 g, 79 % yield). ESMS $_{m/z}$ = 520 $(M+H)^+$. This material was used without purification.

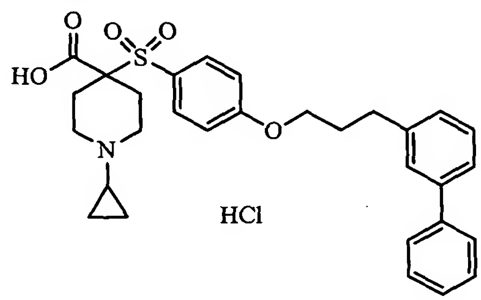
[941] **Part F.** Preparation of:



To a suspension of the crude acid of **Part E** (3.44 g, 6.62 mmol) in DMF (27 mL) were added HOBt (1.52 g, 9.93 mmol), N-methylmorpholine (2.2 mL, 19.9 mmol) and EDC (1.77 g, 9.27 mmol). After heating at 40°C, acid slowly went into solution. When reaction was clear, it was cooled to ambient temperature and THP-hydroxylamine (1.16 g,

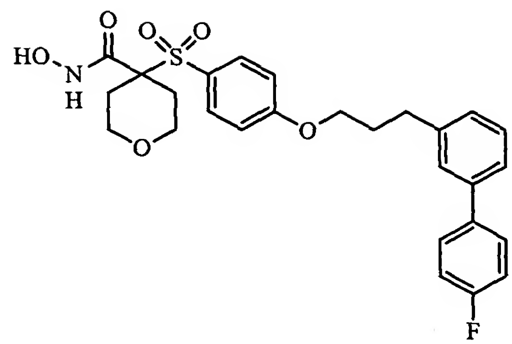
9.93 mmol) was added. The solution was stirred for 18 hr at ambient temperature. The solution was partitioned between ethyl acetate and water. The organic layer was washed with water and brine and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexanes) provided the protected hydroxamate as a crystalline solid (3.20 g, 74 %). NMR δ 0.36 (d, 4H), 1.50-1.92 (m, 8H), 2.05-2.21 (m, 3H), 2.32 (s, 2H), 2.86 (t, 2H), 2.98 (s, 2H), 3.69 (d, 1H), 3.96-4.07 (m, 3H), 5.00 (s, 1H), 6.95 (d, 2H), 7.17 (d, 1H), 7.30-7-43 (m, 6H), 7.54 (d, 2H), 7.73 (d, 2H), 9.41 (s, 1H).

[942] **Part G.** Preparation of:

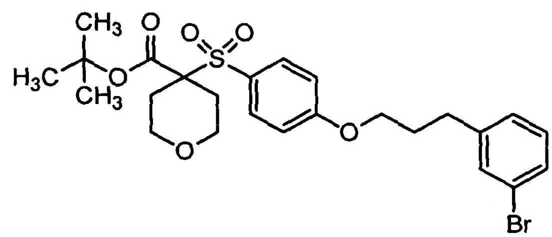


To the semi pure product from **Part F** (3.03 g, 4.89 mmol) in methanol (10 mL) and 1,4-dioxane (10 mL) was added 4M hydrochloric acid in 1,4-dioxane (10 mL) and after stirring 20-30 min the product began to crystallize out. Reverse phase chromatography (on C_{18}, acetonitrile/water) to remove color followed by conversion to HCl salt with methanol and 4N HCl/dioxane then recrystallization from methanol/iso propanol provided 1.95 g (70 %) of the title compound as a hydrochloric acid salt that was colorless. ESMS $_{m/z}$ = 535 $(M+H)^+$. HRMS calcd. for $C_{30}H_{35}N_{20}O_5S$ H: 535.2261 $(M+H)^+$. Found: 535.2270.

[943] **Example 39. Preparation of:**

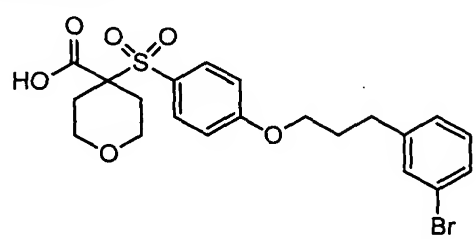


[944] **Part A.** Preparation of:



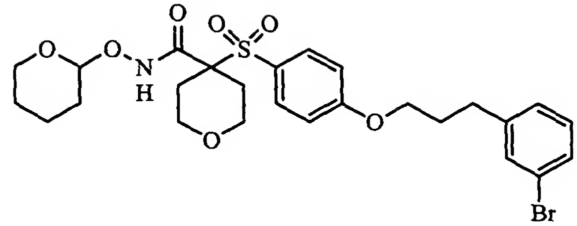
A solution of the alcohol from **Part B, Example 38** (4.4 g, 20.4 mmol), tert-butyl 4-[(4-fluorophenyl)sulfonyl]tetrahydro-2H-pyran-4-carboxylate (5.0 g, 14.6 mmol) and Cs_2CO_3 (9.5 g, 29.2 mmol) in anhydrous dimethylformamide (30 mL) was stirred at 80°C for 30 hr. The reaction was diluted with water (300 mL) and extracted with ethyl acetate (3 times). The combined organic extracts were washed with brine and dried over magnesium sulfate. Crystallization from methylene chloride/hexane gave 6.95 g (88%) of the product as a colorless solid. ESMS $_{m/z}$ = 556 $(M+NH_4)^+$. HRMS calcd. for $C_{25}H_{35}BrNO_6S$ H: 556.1368 $(M+NH_4)^+$. Found: 556.1318.

[945] **Part B.** Preparation of:



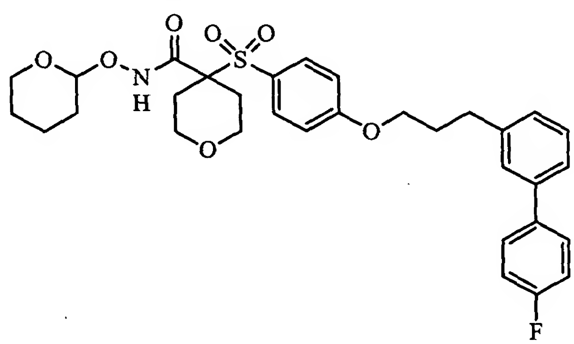
The ester of **Part A** (6.81 g, 12.6 mmol) was hydrolyzed in 1:1 TFA:methylene chloride (50 mL) at ambient temperature for 1.5 hr. The solution was concentrated *in vacuo*, taken up in toluene, concentrated to a colorless solid and dried under high vacuum yielding the acid as an impure white solid (6.28 g, 100 % yield). ESMS $_{m/z}$ = 500 $(M+NH_4)^+$. HRMS calcd. for $C_{21}H_{23}BrO_6SNH_4$: 500.0742 $(M+NH_4)^+$. Found: 500.0761.

[946] **Part C.** Preparation of:



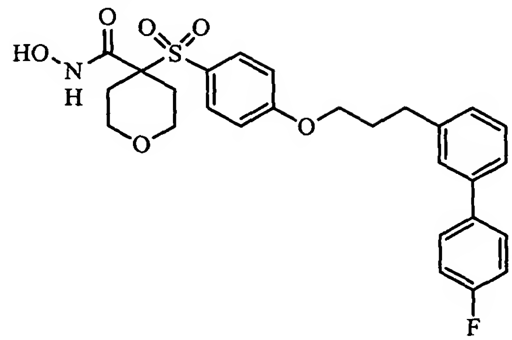
To a suspension of the impure acid of **Part B** (theoretically 12.5 mmol) in anhydrous DMF (25 mL) were added HOBt (2.0 g, 15 mmol), triethylamine (5.2 mL, 37.5 mmol) and EDC (3.4 g, 17.5 mmol). After heating at 40°C for 1 hr, THP hydroxylamine (4.4 g, 37.5 mmol) was added. The solution was stirred for 18 hr at ambient temperature, then at 40°C for 3 hr. The reaction was diluted with water (150 mL) and extracted with ethyl acetate (3 times). The combined organic extracts were washed with brine and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexanes) provided the protected hydroxamate as a viscous oil (4.32 g, 60 %). ESMS $_{m/z}$ = 601 $(M+NH_4)^+$. HRMS calcd. for $C_{26}H_{32}BrNO_7SNH_4$: 601.1410 $(M+NH_4)^+$. Found: 601.1448.

[947] **Part D.** Preparation of:



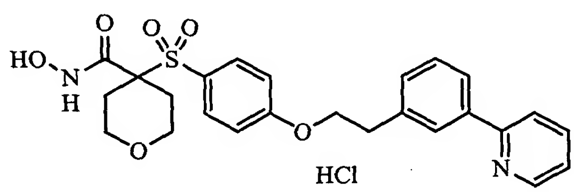
In a vial were combined the aryl bromide from **Part C** (0.20 g, 0.34 mmol) in 1 mL of dimethoxyethyl ether, 4-fluorobenzeneboronic acid (74 mg, 0.53 mmol), palladium tetrakistriphenylphosphine (23 mg, 0.02 mmol) in 0.5 mL of dimethoxyethyl ether and 2M cesium carbonate (0.51 mL, 1.02 mmol). The mixture stirred vigorously at 65°C for 18 hr. The eaction mixture was poured onto 5 mL Chem-Elut tube pre-wetted with 3 mL of water and eluted with 10% ethyl acetate/methylene chloride. Concentration under nitrogen gave 254 mg of crude product that was carried on as is.

[948] **Part E.** Preparation of:

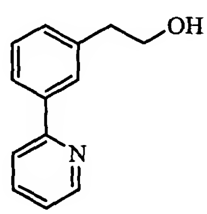


The crude product from **Part D** (254 mg) was taken up in 4M hydrochloric acid in 1,4-dioxane (2 mL) and methanol (1-2 mL) and stirred for 2 hr then concentrated. Material purified by reverse phase chromatography (on C_{18}, acetonitrile/water). Product crystallized upon concentration yielding 108.5 mg (62%) of the title compound as colorless solid. ESMS $_{m/z}$ = 514 $(M+H)^+$. HRMS calcd. for $C_{27}H_{29}FNOS$: 514.1700 $(M+H)^+$. Found: 514.1694 .

[949] **Example 40. Preparation of:**



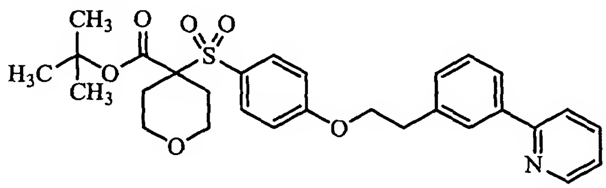
[950] **Part A.** Preparation of:



3-bromophenethyl alcohol (5.0 g, 24.9 mmol) and 2-(tributylstannyl)pyridine (13.6 g, 37.4 mmol) were combined in a round bottom flask with $PdCl_2(PPh_3)_2$ (0.84 g, 1.2 mmol), CuI (0.23 g, 1.2 mmol) and anhydrous THF (100 mL) and heated to reflux. After refluxing overnight, additional $PdCl_2(PPh_3)_2$ (0.84 g, 1.2 mmol) and CuI (0.23 g, 1.2 mmol) were added and the reaction refluxed overnight. The reaction was cooled to ambient

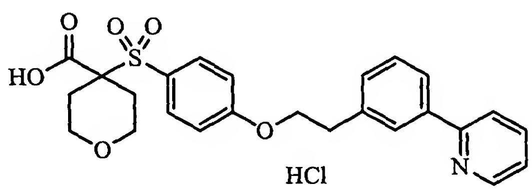
temperature, Norit A charcoal added, the mixture stirred and then filtered through a bed of celite. Chromatography (on silica, ethyl acetate/hexanes) provided the alcohol as an orange oil (2.76 g, 55.8%). ESMS $_{m/z}$ = 200 $(M+H)^+$.

[951] **Part B.** Preparation of:



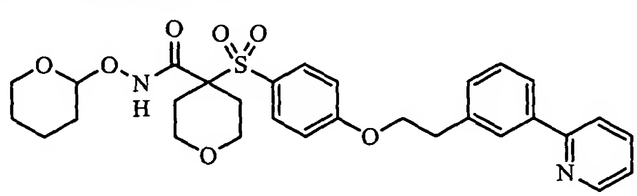
To a solution of the alcohol from **Part A** (2.75 g, 13.8 mmol) in anhydrous dimethylformamide (13 mL) at 0°C was added 60 % sodium hydride (0.58 g, 14.4 mmol) in portions. After completion of the addition, the reaction was stirred at 0°C for 30 min. tert-butyl 4-[(4-fluorophenyl)sulfonyl]tetrahydro-2H-pyran-4-carboxylate (4.51 g, 13.1 mmol) in anhydrous dimethylformamide (10 mL) was added over 15 min. Upon completion of addition, the ice bath was removed and the reaction stirred at ambient temperature. After 1.5 hr the reaction was diluted with water and extracted with ethyl acetate 3 times. The combined organics were washed with saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexanes) provided the product as an off white solid (5.44 g, 79 %). ESMS $_{m/z}$ = 524 $(M+H)^+$.

[952] **Part C.** Preparation of:



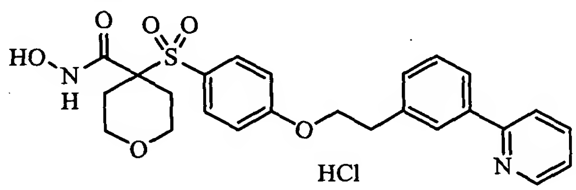
The ester of **Part B** (5.45 g, 10.4 mmol) was hydrolyzed in 1:1 mixture of TFA:methylene chloride (30 mL) at ambient temperature for 8 hr. The solution was concentrated *in vacuo*, taken up in methanol and 4N HCl in dioxane and concentrated. This was repeated to give a viscous oil (6.25 g, > 100 % yield). This material was used without further purification.

[953] **Part D.** Preparation of:



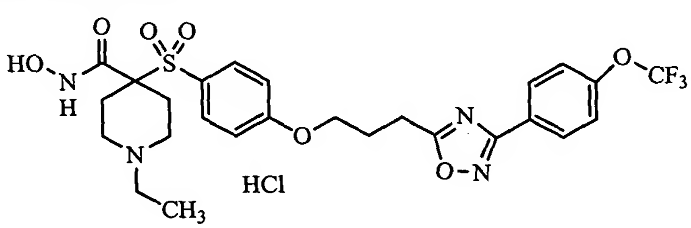
To a suspension of the crude acid of **Part C** (assume 10.4 mmol) in NMP (40 mL) were added HOBt (2.39 g, 15.6 mmol), N-methylmorpholine (3.4 mL, 31.2 mmol) and EDC (2.79 g, 14.6 mmol). After heating at 40°C overnight, HPLC still showed acid to be present so additional added HOBt (2.39 g, 15.6 mmol), N-methylmorpholine (3.4 mL, 31.2 mmol) and EDC (2 . 7 9 g, 14.6 mmol) were added. After 1 hr at 40°C, THP hydroxylamine (3.66 g, 31.2 mmol) was added. After 1 hr, the solution was diluted with water and extracted with ethyl acetate 3 times. The combined organic layers were washed with brine and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexanes) provided the protected hydroxamate as a colorless foam (5.05 g, 85.7). ESMS $_{m/z}$ = 567 $(M+H)^+$.

[954] **Part E.** Preparation of:



To the product from **Part D** (5 . 0 5 g , 8.91 mmol) in methanol (15 mL) and 1,4-dioxane (15 mL) was added 4M hydrochloric acid in 1,4-dioxane (15 mL) and after stirring 1 hr reaction was complete. Concentration followed by crystallization from methanol/iso-propanol provided 3.88 g (84 %) of the title compound as a hydrochloric acid salt that was colorless. ESMS $_{m/z}$ = 483 $(M+H)^+$. HRMS calcd. for $C_{25}H_{27}N_2O_6S$ H: 483.1584 $(M+H)^+$. Found: 483.1585.

[955] **Example 41. Preparation of 1-ethyl-N-hydroxy 4-{[4-(3-{3-[4-(trifluoromethoxy)phenyl]-1,2,4-oxadiazol-5-yl}propoxy)phenyl]sulfonyl}piperidine-4-carboxamide hydrochloride.**



[956] **Part A.** To a slurry of ethyl 4-[(4-fluorophenyl)sulfonyl]-4-piperidinecarboxylate, monohydrochloride (14.06 g, 40 mmol) in dimethylacetamide (80

mL) were added potassium carbonate (13.82 g, 100 mmol) and iodoethane (3.36 mL, 42 mmol). The slurry was stirred at ambient temperature. After 3 hr the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, methylene chloride/hexanes) provided the N-ethyl piperidine as a white solid (13.05 g, 95%).

[957] **Part B.** In dry equipment under nitrogen, potassium trimethylsilanolate (10.52 g, 73.8 mmol) was dissolved in dimethylsulfoxide (40 mL) and gamma-butyrolactone (4.26 mL, 55.4 mmol) was added over 5 min while the reaction temperature rose to 49 C. After stirring at ambient temperature for 90 min, sodium hydride (2.2 g of a 60% oil dispersion, 55.4 mmol) was added portion wise over 20 min and the reaction temperature rose to 38°C. Gas evolution was also observed. After stirring at ambient temperature for 40 min, a solution of the N-ethyl piperidine from **Part A** (12.66 g, 36.9 mmol) in dimethylsulfoxide (10 mL) was added over 10 min as the reaction rose to 8°C. The reaction was stirred at ambient temperature for t30 min. The slurry was slowly poured into ice water (400 mL) and then extracted with hexanes (100 mL) two times followed by a diethyl ether extraction (100 mL). The aqueous layer was chilled to 5°C and the pH adjusted to 7 with concentrated hydrochloric acid. The aqueous solution was extracted with methylene chloride (150 mL) until there was no UV activity in the extract. The combined methylene chloride extracts were washed with saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The solid was recrystallized from isopropanol (65 mL) to give the butyric acid as a white solid (8.2 g, 52%). LCMS $_{m/z}$ = 428 $[M+H]^+$.

[958] **Part C.** In dry equipment under nitrogen, the butyric acid from **Part B** (5.12 g, 12.0 mmol) was dissolved in dry dimethylacetamide (20 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (2.43 g, 18.0 mmol), triethylamine (3.34 mL, 24.0 mmol), 4-(trifluoromethoxy)benzamidoxime (3.96 g, 18.0 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.6 g, 24.0 mmol). After 24 hr at 70°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and

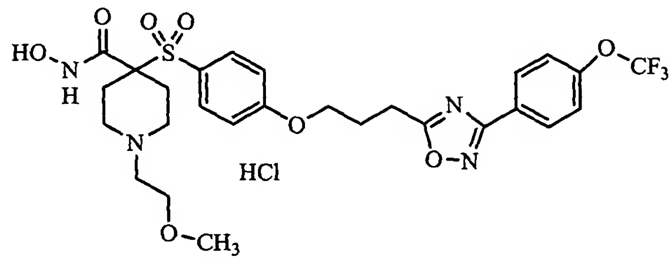
concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/methanol/hexanes) provided the oxadiazole as a light yellow solid (5.05 g, 69%). LCMS $_{m/z}$ = 612 $[M+H]^+$.

[959] **Part D.** A slurry of the oxadiazole from **Part C** (4.9 g, 8.02 mmol), 2.5N sodium hydroxide (9.6 mL, 24.06 mmol) and sodium hydroxide (1.28 g, 32.08 mmol) in isopropanol (40 ml) were stirred at 70°C for 7 hr. The heat was removed and the reaction diluted with water (100 ml) and chilled to 5°C. The pH was adjusted to 7 with concentrated hydrochloric acid. The solids were filtered, washed with hexanes, and dried *in vacuo* to give the carboxylic acid as a white solid (4.54 g, 97%). LCMS $_{m/z}$ = 584 $[M+H]^+$.

[960] **Part E.** In dry equipment under nitrogen, the carboxylic acid from **Part D** (4.5 g, 7.72 mmol) was dissolved in dry dimethylacetamide (15 ml) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (1.56 g, 11.6 mmol), triethylamine (3.22 mL, 23.2 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (1.35 g, 11.6 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.96 g, 15.4 mmol). After 29 hr at 50°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/methanol/hexanes) provided the THP hydroxamate as a light yellow solid (2.4 g, 46%). LCMS $_{m/z}$ = 683 $[M+H]^+$.

[961] **Part F.** To the THP hydroxamate from **Part E** (2.3 g, 3.37 mmol) was added 4N HCl dioxane solution (8.4 mL, 33.7 mmol) and methanol (0.84 mL). The slurry became very thick. Diethyl ether (50 ml) was added to and after 1 hr at ambient temperature the reaction was filtered under nitrogen. The solids were washed with diethyl ether (150 ml) under nitrogen and dried *in vacuo* over phoshorus pentoxide to give the title compound as a white solid (1.92 g, 91%). HRMS (ES+) $M+H^+$ calculated for $C_{26}H_{29}N_4O_7S_1F_3$: 599.1787, found 599.1766.

[962] **Example 42. Preparation of:**



[963] **Part A.** In dry equipment under nitrogen, potassium trimethylsilanolate (42.76 g, 0.3 mol) was dissolved in dimethylsulfoxide (170 mL) and gamma-butyrolactone (17.31 mL, 0.225 mol) was added over 5 min while the reaction temperature rose to 49 C. After stirring at ambient temperature for 90 min, sodium hydride (9.0 g of a 60% oil dispersion, 0.225 mol) was added portion wise over 20 min and the reaction temperature rose to 38°C. Gas evolution was also observed. After stirring at ambient temperature for 40 min, a solution of ethyl 4-[(4-fluorophenyl)sulfonyl]-1-(2-methoxyethyl)piperidine-4-carboxylate (56 g, 0.15 mol) in dimethylsulfoxide (20 mL) was added over 10 mins as the reaction rose to 38°C. The reaction was stirred at ambient temperature for 30 min. The slurry was slowly poured into ice water (1.1 L) and then extracted with hexanes (300 mL) two times followed by a diethyl ether extraction (200 mL). The aqueous layer was chilled to 5°C and the pH adjusted to 7 with concentrated hydrochloric acid. The aqueous solution was extracted with methylene chloride (150 mL) until there was no UV activity in the extract. The combined methylene chloride extracts were washed with saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The solid was recrystallized from methanol (200 mL) to give the butyric acid as a white solid (34.8 g, 51%). LCMS $_{m/z}$ = 458 $[M+H]^+$.

[964] **Part B.** In dry equipment under nitrogen, the butyric acid from **Part A** (19.19 g, 42.0 mmol) was dissolved in dry dimethylformamide (100 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (8.5 g, 63.0 mmol), triethylamine (11.7 mL, 84.0 mmol), 4-(trifluoromethoxy)benzamidoxime (13.9 g, 63.0 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (16.1 g, 84.0 mmol). After 24 hr at 70°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated $NaHCO_3$, saturated sodium chloride solution, dried

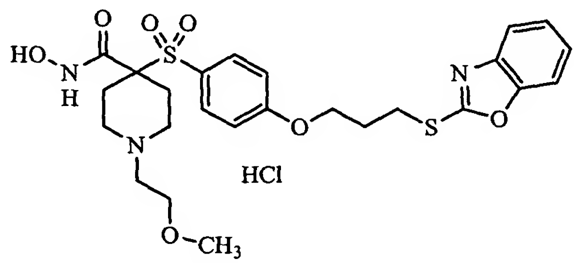
over Na_2SO_4, filtered, and concentrated *in vacuo*. The solid was recrystallized from methanol (35 mL) to give the oxadiazole as an off white solid (17.86 g, 66%). LCMS $_{m/z}$ = 642 $[M+H]^+$.

[965] **Part C.** A slurry of the oxaziazole from **Part B** (16.9 g, 26.4 mmol), 2.5N sodium hydroxide (31.6 mL, 79.1 mmol) and sodium hydroxide (4.22 g, 105.5 mmol) in isopropanol (30 mL) were stirred at 70°C for 7 hr. The heat was removed and the reaction diluted with water (150 mL) and chilled to 5°C. The pH was adjusted to 7 with concentrated hydrochloric acid. The solids were filtered, washed with hexanes, and dried *in vacuo* to give the carboxylic acid as a white solid (15.78 g, 98%). LCMS $_{m/z}$ = 614 $[M+H]^+$.

[966] **Part D.** In dry equipment under nitrogen, the carboxylic acid from **Part C** (15.7 g, 25.6 mmol) was dissolved in dry dimethylformamide (70 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (5.19 g, 38.4 mmol), triethylamine (10.7 mL, 76.8 mmol), O-(tetrahydro-2H-pyran2-yl)hydroxylamine (5.99, 51.2 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (10.8 g, 56.3 mmol). After 12 hr at 40°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the THP hydroxamate as a white foam (14.94 g, 82%). LCMS $_{m/z}$ = 713 $[M+H]^+$.

[967] **Part E.** To the THP hydroxamate from **Part D** (14.88 g, 20.9mmol) was added 4N HCl dioxane solution (52 mL, 209.0 mmol) and methanol (5.2 mL). The slurry became very thick. Dioxanes (50 mL) and diethyl ether (100 mL) were added to facilitate stirring. After 1 hr at ambient temperature the reaction was filtered under nitrogen. The solids were washed with acetonitrile (100 mL) under nitrogen and dried *in vacuo* over phoshorus pentoxide to give the title compound as a white solid (13.25 g, 95%). HRMS (ES+) M+ H^+ calculated for $C_{27}H_{31}N_4O_8S_1F_3$: 629.1893, found 629.1913.

[968] **Example 43. Preparation of 4-({4-[3-(1,3-benzoxazol-2-ylthio)propoxy]phenyl}sulfonyl)-N-hydroxy-1-(2-methoxyethyl)piperidine-4-carboxamide hydrochloride.**



[969] **Part A.** A solution of 1-benzyl 4-tert-butyl 4-[(4-fluorophenyl)sulfonyl]piperidine-1,4-dicarboxylate (16.0 g, 33.5 mmol) in methanol/tetrahydropyran was hydrogenated for 1 hr at 5 psi in the presence of 5% Pd/C. The solution was filtred to remove the catalyst and concentrated *in vacuo*. 11.0 g (95% yield) of the amine was obtained as a white solid.

[970] **Part B.** The solution of the amine of **Part A** (11.0 g, 32.1 mmol) in N,N-dimethylformamide (100 mL) was cooled to 0°C on an ice bath. Potassium carbonate (13.3 g, 96.4 mmol) and 2-bromoethylmethyl ether (7.54 mL, 80.2 mmol) were added to the chilled solution. The solution was stirred for 72 hr at ambient temperature and partitioned between ethyl acetate and water. The organic layer was washed with water and saturated sodium chloride and dried over sodium sulfate. 14.5 g of the desired alkylated amine was obtained as an orange oil by concentration *in vacuo*.

[971] **Part C.** To a solution of propanediol (10.44 mL, 144 mmol) in 1-methyl-2-pyrrolidinone (40 mL) cooled to 0°C was added sodium hydride (60% suspension in mineral oil, 3.85 g, 96.3 mmol). The alkylated amine from **Part B** (14.5 g, 32.1 mmol) was dissolved into 1-methyl-2-pyrrolidinone (50 mL) and added dropwise to the cooled solution. The solution was stirred at ambient temperature for 1 hr. The reaction was quenched by adding water and partitioned between ethyl acetate and water. The organic layer was washed with water and saturated sodium chloride and dried over sodium sulfate. The desired alcohol was obtained as an orange oil by concentration *in vacuo*. MS(CI) MH^+ calculated for $C_{22}H_{35}NO_7S$: 457, found 457.

[972] **Part D.** To a solution of the alcohol of **Part C** (32.1 mmol) in methylene chloride (100 mL) was added triethylamine (4.92 mL, 35.3 mmol). The solution was

cooled to 0°C and methanesulfonyl choride (2.56 mL, 33.0 mmol) was added dropwise. After 1 hr the reaction was concentrated *in vacuo*. The residue was dissolved into ethyl actate and washed with water, saturated sodium bicarbonate and saturated sodium chloride and dried over sodium sulfate. The solution was concentrated *in vacuo* to provide 17.5 g of the desired mesylate. MS(CI) MH^+ calculated for $C_{23}H_{37}NO_9S_2$: 536, found 536.

[973] **Part E.** To a solution of 2-mercaptobenzoxazole (4.86 g, 32.1 mmol) in N,N-dimethylformamide (30 mL) cooled to 0°C was added sodium hydride (60% suspension in mineral oil, 1.54 g, 38.5 mmol). After 30 min the mesylate of **Part D** (17.5 g, 32.1 mmol) in N,N-dimethylformamide (30 mL) was added dropwise. The solution was heated at 60°C for 4 hr and at 45°C for 18 hr. The solution was returned to ambient temperature and partitioned between ethyl acetate and water. The organic layer was washed with water and saturated sodium chloride and dried over sodium sulfate. Chromotography (ethyl acetate, on silica) provided the mercaptobenzoxazole as a colorless oil (7.3 g, 39% yield over four steps). MS(CI) MH^+ calculated for $C_{29}H_{38}N_2O_7S_2$: 591, found 591.

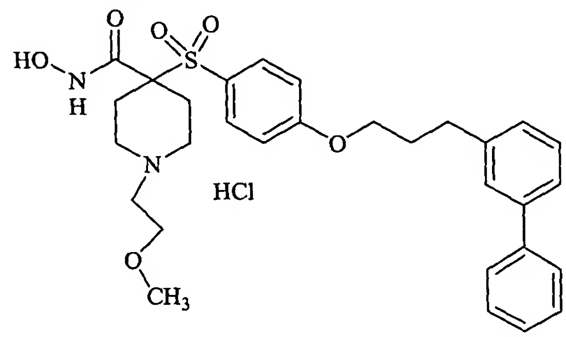
[974] **Part F.** To a solution of the mercaptobenzoxazole of **Part E** (7.3 g, 12.4 mmol) was added trifluoroacetic acid (20 mL) and the solution stirred for 3 hr. The solution was concentrated *in vacuo* and azotroped with toluene to provide the acid as an oil. The material was carried on without additional purification. MS(CI) MH^+ calculated for $C_{25}H_{30}N_2O_7S_2$: 535, found 535.

[975] **Part G.** To a solution of the acid of **Part F** (12.4 mmol) in N,N-dimethylformamide (50 mL) were added 1-hydroxybenztriazole (2.01 g, 14.9 mmol), 4-methylmorpholine (6.82 mL, 62 mmol) and tetrahydropyranylamine (2.18 g, 18.6 mmol). After30 min 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.33 g, 17.4 mmol) was added. The solution was heated to 65°C for 2 hr. The solution was partitioned between ethyl acetate and water. The organic layer was washed with water and saturated sodium chloride and dried over sodium sulfate. Chromotography (ethyl acetate/methanol, on silica) provided the protected hydroxamate as a colorless oil (3.9 g, 50 % yield). MS(CI) MH^+ calculated for $C_{30}H_{39}N_3O_8S_2$: 634, found 634.

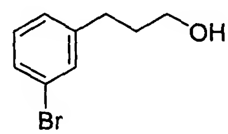
[976] **Part H.** To a solution of the protected hydroxamate of **Part G** (3.9 g, 6.2 mmol) in 1,4-dioxane (10 mL) was added 4M hydrochloric acid in 1,4-dioxane (10 mL). The reaction was complete after 1 hr. The solution was concentrated *in vacuo*. The

residue was purified via reverse phase chromatography (acetonitrile/water, on silica) to provide the title compound as a white solid (1.49 g, 41% yield). MS(CI) MH^+ calculated for $C_{25}H_{31}N_3O_7S_2$: 550, found 550. HRMS calculated for $C_{25}H_{31}N_3O_7S_2$: 550.1682, found 550.1668. Analytical calculation for $C_{25}H_{31}N_3O_7S_2.HCl.H_2O$: C, 49.70; H, 5.67; N, 6.96; S, 10.62; Cl, 5.87. Found: C, 49.91; H, 6.03; N, 6.74; S, 10.75; Cl, 6.35.

[977] **Example 44. Preparation of:**

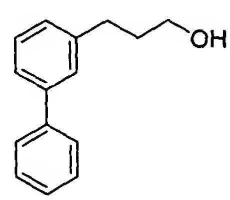


[978] **Part A.** Preparation of:



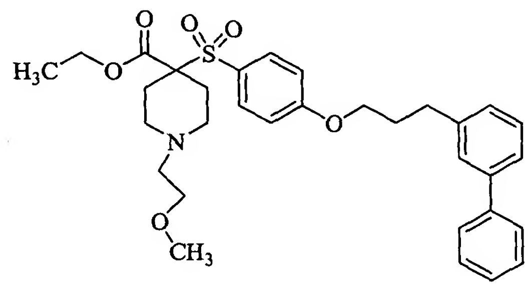
To a solution of 3-(3-bromophenyl)propionic acid (15.0 g, 65.5 mmol) in anhydrous THF (200 mL) at 5°C was added, via addition funnel, 1.0 M $BH_3 \cdot THF$ (200 mL, 200 mmol). The reaction temperature was kept below 14°C during the addition of the $BH_3 \cdot THF$. After all the $BH_3 \cdot THF$ was added, the reaction was refluxed for 22 hr and then quenched with water (100 mL) and 1N HCl (300 mL). The solution was saturated with sodium chloride and extracted with ethyl acetate (3x300 mL). The organic extract was washed with brine, dried over magnesium sulfate, and concentrated providing 14.4 g (100%) of crude alcohol as a colorless oil. NMR($CDCl_3$) δ 1.82-1.89 (m, 2H), 2.67 (t, 2H), 3.64 (t, 2H), 7.11-7.15 (m, 1H), 7.29-7.31 (m, 1H), 7.34 (s, 1H).

[979] **Part B.** Preparation of:



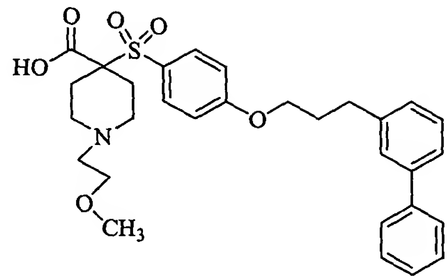
In a flask were combined the alcohol from **Part A** (65.5 mmol), phenyl boronic acid (12.0 g, 98.2 mmol), palladium tetrakistriphenylphosphine (3.8 g, 3.3 mmol), 2M cesium carbonate (98 mL, 196 mmol) and dimethoxyethylether (100 mL). The mixture was stirred vigorously under nitrogen at reflux overnight. The reaction was cooled to ambient temperature, poured into water (300 mL) and extracted 3 times with ethyl acetate. The combined organic extracts were washed with brine and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate / hexane) provided the coupled product as a golden oil (11.95 g, 86.0 %). NMR($CDCl_3$) δ 1.91-1.98 (m, 2H), 2.77 (t, 2H), 3.71 (t, 2H), 7.19 (d, 1H), 7.31-7.38 (m, 2H), 7.41-7.45 (m, 4H), 7.58 (d, 2H).

[980] **Part C.** Preparation of:



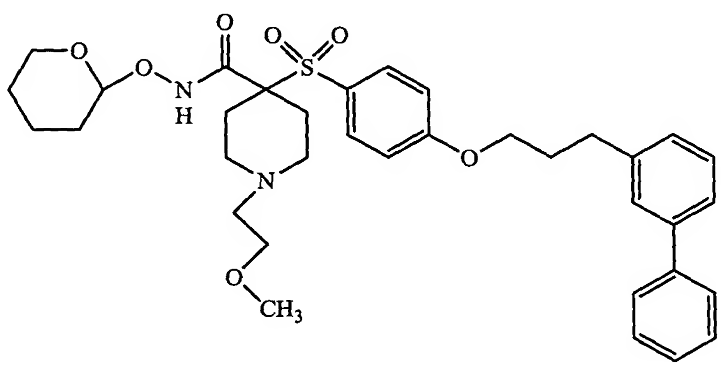
To a solution of the alcohol from **Part B** (11.9 g, 56.1 mmol) in anhydrous dimethylformamide (56 mL) at 0°C was added 60% sodium hydride (2.55 g, 63.8 mmol) in portions. After completion of the addition, the reaction was stirred at 0°C for 15 min then ambient temperature for 15 min. The reaction was cooled to 0°C and ethyl 4-[(4-fluorophenyl)sulfonyl]-1-(2-methoxyethyl)piperidine-4-carboxylate (19.0 g, 51 mmol) in anhydrous dimethylformamide (60 mL) was added slowly. Upon completion of addition, the ice bath was removed and the reaction stirred at ambient temperature overnight. Reaction was poured into water (1 L) and extracted with ethyl acetate (800 mL). The combined organics were washed with water (2x500 mL) and brine and dried over magnesium sulfate. Concentration gave 34.4 g of crude material. This material was used without purification.

[981] **Part D.** Preparation of:



The impure ester of **Part C** (34.4 g, 51 mmol theoretical) was hydrolyzed in 41 mL of ethanol, 41 mL of 1,4-dioxane and 26.5 mL of 6 N NaOH at 60°C. The solution was poured into water and extracted with ether to remove color. Acidification with 1N HCl caused precipitation of the acid which was collected by filtration and washed with water, ethyl acetate and hexane then dried under high vacuum yielding the acid as an off white solid (18.8 g, 68.6% yield). NMR (CD_3OD w/ K_2CO_3) δ 1.98 (t, 2H), 2.07-2.19 (m, 4H), 2.32 (d, 2H), 2.48 (t, 2H), 2.85-2.95 (m, 4H), 3.25 (s, 3H), 4.06 (t, 2H), 7.04 (d, 2H), 7.20 (d, 1H), 7.27-7.48 (m, 5H), 7.54 (d, 2H), 7.78 (d, 2H). ESMS *m/z* = 538 $(M+H)^+$.

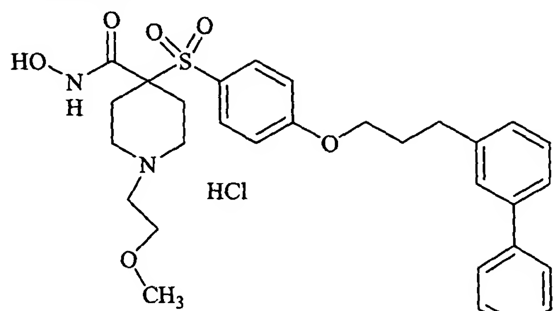
[982] **Part E.** Preparation of:



To the acid of **Part D** (12.7 g, 23.6 mmol), HOBt (5.42 g, 35.4 mmol), EDC (6.30 g, 3.30 mmol) in a flask under N_2 was added 70 mL anhydrous DMF. The mixture was heated to 60°C and triethylamine (9.85 mL, 70.8 mmol) was added. After heating at 60°C for 1 hr, THP-hydroxylamine (4.14 g, 35.4 mmol) was added. The solution was stirred for 16.5 hr at 60°C. The solution was partitioned between ethyl acetate (300 mL) and water (500 mL). The organic layer was washed with brine and dried over magnesium sulfate. Concentration provided the protected hydroxamate as an oil (14.86 g, 98.7 %). NMR($CDCl_3$) δ 1.55-1.90 (m, 6H), 2.09-2.27 (m, 8H), 2.50 (t, 2H), 2.87 (t, 2H), 2.90-2.98

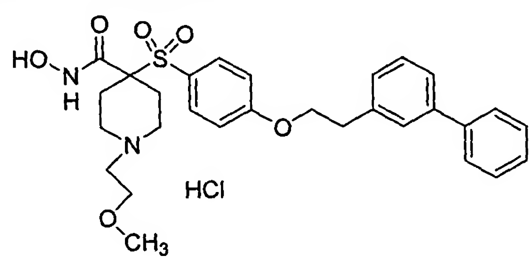
(m, 2H), 3.32 (s, 3H), 3.42 (t, 2H), 3.7.1 (d, 1H), 3.98 (d, 1H), 4.03 (t, 2H), 4.99 (s, 1H), 6.97 (d, 2H), 7.19 (d, 1H), 7.30-7.46 (m, 6H), 7.57 (d, 2H), 7.77 (d, 2H), 9.42 (s, 1H). ESMS m/z = 637 $(M+H)^+$.

[983] **Part F.** Preparation of:

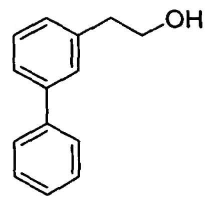


To the product from **Part E** (14.7 g, 23.1 mmol) in methanol (23 mL) and 1,4-dioxane (23 mL) was added 4M hydrochloric acid in 1,4-dioxane (23 mL) and after stirring 1 hr, material dripped in to stirring IPA, let stand overnight. Collection of solid under N_2 followed by washing with IPA and hexane then drying on high vacuum over P_2O_5 provided 12.5 g (91.8 %) of the title compound as a hydrochloric acid salt that was colorless. NMR(DMSO) δ 2.05-2.25 (m, 4H), 2.74, (t, 2H), 2.81 (t, 2H), 3.18-3.26 (m, 4H), 3.39 (s, 3H), 3.51-3.61 (m, 4H), 4.09 (t, 2H), 7.15 (d, 2H), 7.22 (d, 1H), 7.29-7.49 (m, 6H), 7.58 (d, 2H), 7.45 (d, 2H).. ESMS m/z = 553 $(M+H)^+$. HRMS calcd. for $C_{30}H_{35}N_2O_5S$ H: 553.2369 $(M+H)^+$. Found: 553.2372.

[984] **Example 45. Preparation of:**

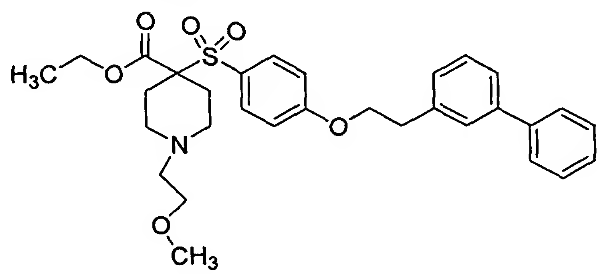


[985] **Part A.** Preparation of:



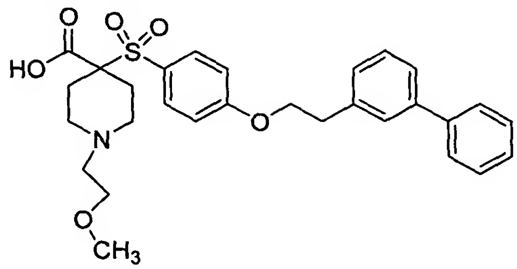
In a flask were combined the 3-bromophenethyl alcohol (17.5 g, 87.1 mmol), phenyl boronic acid (12.7 g, 104.5 mmol), palladium tetrakistriphenylphosphine (2.0 g, 1.74 mmol), 2M cesium carbonate (105 mL, 210 mmol) and dimethoxyethylether (105 mL). Mixture stirred vigorously under nitrogen at reflux overnight. After cooling to ambient temperature, poured mixture into water (400 mL) and extracted with ethyl acetate (2x400 mL). Combined organics were washed with brine and dried over magnesium sulfate. Silica gel chromotography (ethyl acetate / hexane) provided the coupled product as a crystalline solid (15.04 g, 87.3 %). NMR($CDCl_3$) δ 2.95 (t, 2H), 3.93 (q, 2H), 7.19-18 (m, 2H), 7.31-7.51 (m, 5H), 7.58 (d, 2H). GCMS EI+ 198 (M+).

[986] **Part B.** Preparation of:



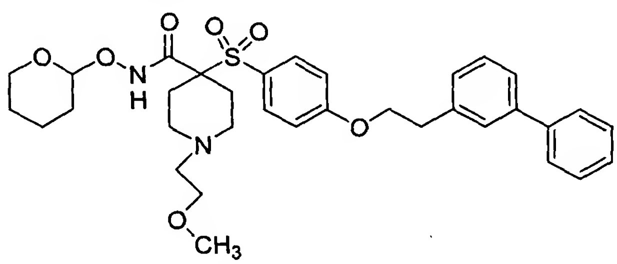
To a solution of the alcohol from **Part A** (14.9 g, 75.2 mmol) in anhydrous dimethylformamide (70 mL) at 0°C was added 60 % sodium hydride (3.0 g, 75.2 mmol) in portions. After completion of the addition, the reaction was stirred at 0°C for 30 min. ethyl 4-[(4-fluorophenyl)sulfonyl]-1-(2-methoxyethyl)piperidine-4-carboxylate (33.6 g, 90.2 mmol) in anhydrous dimethylformamide (50 mL) at 5°C was added slowly. Upon completion of addition let reaction slowly warm up overnight. Reaction was poured into water (700 mL) and extracted with ethyl acetate (3x500 mL). The combined organics were washed with brine and dried over sodium sulfate. Concentration gave 50.6 g of crude material. This material was used without purification. ESMS $m/z = 552\ (M+H)^+$.

[987] **Part C.** Preparation of:



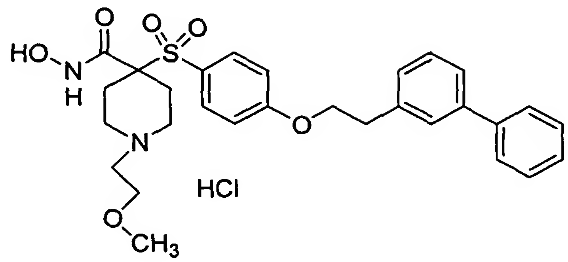
The impure ester of **Part B** (75.2 mmol theoretical) was hydrolyzed in 75 mL of ethanol, 75 mL of 1,4-dioxane and 50 mL of 6 N NaOH at 60 C for 2.5 hr. The solution was poured into water and extracted with ether to remove color. Acidification with 1N HCl caused precipitation of the acid which was collected by filtration and washed with water, ethyl acetate and diethyl ether then dried under high vacuum yielding the acid as a white solid (31.7 g, 80.6% yield). ESMS *m/z* = 524 $(M+H)^+$. HRMS calcd. for $C_{29}H_{34}NO_6S$: 524.2101 $(M+H)^+$. Found: 524.2075.

[988] **Part D.** Preparation of:



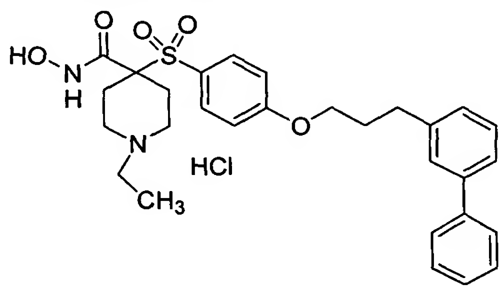
The acid of **Part C** (31.6 g, 60.4 mmol), HOBt (13.9 g, 90.6 mmol), EDC (16.2 g, 84.6 mmol), triethylamine (25.2 mL, 181 mmol) and THP-hydroxylamine (10.6 g, 90.6 mmol) were stirred in anhydrous dimethylformamide (200 mL) under N_2 at 60°C overnight. After cooling to room temperature solution was poured into 1.6 L of ice water and extracted with ethyl acetate (2x1 L). The organic layer was washed with brine and dried over sodium sulfate. Silica gel chromatography (2.0M NH_3 in MeOH/ethyl acetate/hexane) gave the desired product as a colorless foam (30.89 g, 82%). ESMS *m/z* = 623 $(M+H)^+$. HRMS calcd. for $C_{34}H_{43}N_2O_7S$: 623.2786 $(M+H)^+$. Found: 623.2793.

[989] **Part E.** Preparation of:

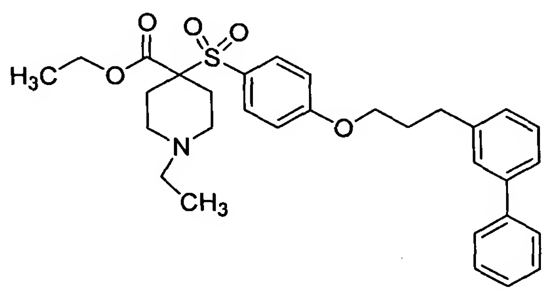


To the product from **Part D** (30.7 g, 49.3 mmol) in methanol (49 mL) and 1,4-dioxane (49 mL) was added 4N HCl in dioxane (50 mL). Material concentrated after 1 hr and crystallized from methanol providing the desired product as a colorless crystalline solid (25.6 g, 90.2%). ESMS *m/z* = 539 $(M+H)^+$. HRMS calcd. for $C_{29}H_{35}N_2O_6S$: 539.2210 $(M+H)^+$. Found: 539.2187.

[990] **Example 46. Preparation of:**



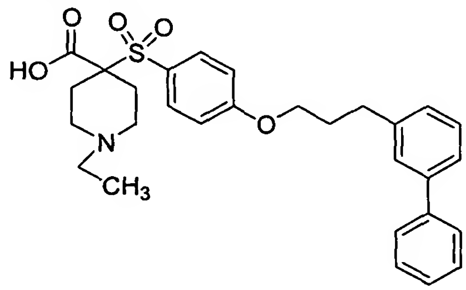
[991] **Part A.** Preparation of:



To a solution of the alcohol from **Example 38, Part B** (12.0 g, 56.1 mmol) in anhydrous dimethylformamide (50 mL) at 0°C was added 60 % sodium hydride (2.58 g, 64.5 mmol) in portions. After completion of the addition, the reaction was stirred at 0°C for 15 min then ambient temperature for 15 min. The reaction was cooled to 0°C and ethyl 1-ethyl-4-[(4-fluorophenyl)sulfonyl]piperidine-4-carboxylate (17.7 g, 51.6 mmol) in anhydrous

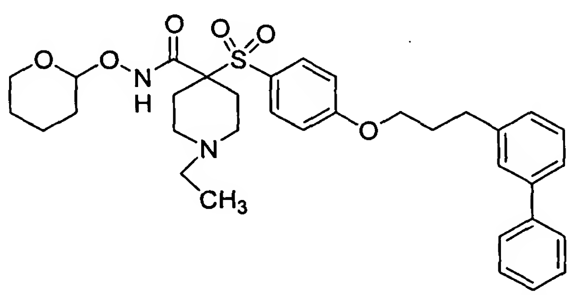
dimethylformamide (60 mL) was added slowly. Upon completion of addition, ice bath was removed and reaction stirred at ambient temperature overnight. Reaction was poured into water and extracted with ethyl acetate 2 times. The combined organics were washed with water 2 times and brine and dried over sodium sulfate. Concentration gave 34.4 g of crude material. This material was used without purification. ESMS m/z = 536 $(M+H)^+$.

[992] **Part B.** Preparation of:



The impure ester of **Part A** (51.6 mmol theoretical) was hydrolyzed in 50 mL of ethanol, 50 mL of 1,4-dioxane and 34.4 mL of 6 N NaOH at 60°C. After cooling to room temperature, the solution was poured into water (500 mL) and extracted with ether (2x250 mL) to remove color. Acidification with 1N HCl caused precipitation of the acid which was collected by filtration and washed with water, ethyl acetate and hexane then dried under high vacuum yielding the acid as an off white solid (18.4 g, 70% yield). ESMS m/z = 508 $(M+H)^+$. HRMS calcd. for $C_{29}H_{34}NO_5S$ H: 508.2152 $(M+H)^+$. Found: 508.2176.

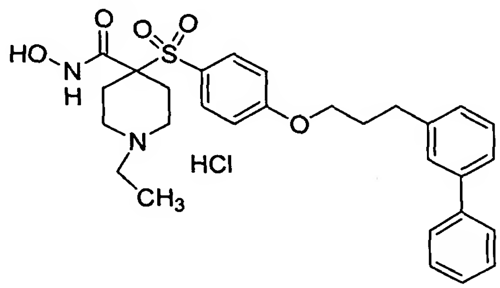
[993] **Part C.** Preparation of:



The acid of **Part B** (18.0g, 35.4 mmol), HOBt (8.12 g, 53.1 mmol), EDC (9.47 g, 49.6 mmol), triethylamine (14.8 mL, 106.2 mmol) and THP-hydroxylamine (6.21g, 53.1 mmol) were stirred in anhydrous dimethylformamide (110 mL) under N_2 at 60°C overnight. After cooling to room temperature, the solution was poured into water (600 mL) and extracted with ethyl acetate. The organic layer was washed with water and brine and dried over sodium sulfate. Silica gel chromatography (2.0M NH_3 in MeOH/ethyl

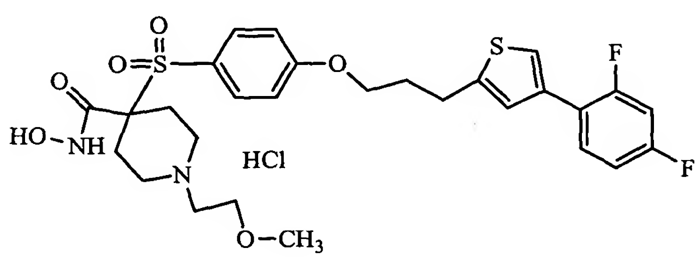
acetate/hexane) gave the desired product as a colorless foam (11.0 g, 51%). ESMS *m/z* = 607 $(M+H)^+$. HRMS calcd. for $C_{34}H_{43}N_2O_6S$: 607.2836 $(M+H)^+$. Found: 607.2829

[994] **Part D.** Preparation of:



To the product from **Part C** (10.8 g, 17.8 mmol) in methanol (18 mL) and 1,4-dioxane (18 mL) was added 4M hydrochloric acid in 1,4-dioxane (18 mL) and after stirring 1 hr, material concentrated. Co-crystallized with another batch from MeOH/4N HCl/dioxane. Collection of solid followed by washing with methanol then drying on high vac provided 11.51 g (88 %) of the title compound as a hydrochloric acid salt that was colorless. ESMS *m/z* = 523 $(M+H)^+$. HRMS calcd. for $C_{29}H_{35}N_2O_5S$ H: 523.2261 $(M+H)^+$. Found: 523.2224.

[995] **Example 47. Preparation of 4-[(4-{3-[4-(2,4-difluorophenyl)thien-2-l]propoxy}phenyl) sulfonyl]-N-hydroxy-1-(2-methoxyethyl)piperidine-4-carboxamide hydrochloride.**



[996] **Part A.** A round bottom flask was charged with 4-bromo-2-thiophene carboxaldehyde (Aldrich, 55.8 g, 292 mmol), 2,4-difluorophenyl boronic acid (Aldrich, 60.0 g, 380 mmol), tetrakis-triphenylphosphine palladium (Aldrich, 16.9 g, 14.6 mmol), 2 M $Na_2CO_3{\cdot}_{aq}$ (190 ml, 380 mmol), and ethylene glycol-dimethyl ether (Aldrich, 500 ml). The reaction was heated to 80°C and stirred for 5 hr. The reaction suspension was then poured into a mixture of methylene chloride (500 ml) and ice water (500ml). The organic

layer was separated and washed with water (2x-200 ml) and brine (1x-300 ml) then dried over Na_2SO_4 and concentrated to afford the thiophene phenyl adduct as a brown oil. Silica gel purification (hexanes/ethyl acetate) yielded a white solid (34.2 g, 52 % yield). ^{1}H NMR showed the desired compound.

[997] **Part B.** A solution of triethyl phosphonoacetate (Aldrich, 24.2 g, 108 mmol) in tetrahydrofuran (100 ml) was cooled to –78°C. A 1.6 M *n*-butyllithium solution in hexanes (68 ml, 108 mmol) was slowly dripped in then the reaction stirred for 30 min at –78°C. A solution of the thiophene phenyl carboxaldehyde product from **Part A** in tetrahydrofuran (100 ml) was slowly dripped in. The dry ice bath was removed and the reaction stirred as it came to ambient temperature overnight. The mixture was diluted with water (200 ml) to quench. The organic layer was separated and washed with water (2x-200 ml) and brine (1x- 300 ml) then dried over Na_2SO_4 and concentrated to afford a tan solid. This solid was recrystallized from warm methanol to yield a light yellow solid (16.1 g, 56 % yield). ^{1}H NMR showed the desired compound.

[998] **Part C.** A solution of the ethyl ester olefin of **Part B** (16 g, 54.4 mmol) in methylene chloride was cooled to 0°C. A 1.0 M solution of lithium aluminum hydride was dripped in slowly, then the reaction continued stirring for 45 min at 0°C. A saturated solution of $NH_4Cl\cdot_{aq}$ was dripped in to quench, followed by a solution of sodium, potassium tartrate $_{aq}$ (10 ml). After stirring for 30 min, Na_2SO_4 (40 g) was added. The mixture was filtered and concentrated to afford a yellow oil (16.8 g, 100^+ % yield). ^{1}H NMR showed the desired compound along with impurities.

[999] **Part D.** A hydrogenation flask was charged with the crude hydroxy olefin residue from **Part C** (~54.4 mmol) was dissolved in tetrahydrofuran (125 ml) and methanol (20 ml). Nitrogen gas was bubbled through for 15 min then 10% Pd/C catalyst (Aldrich, 50% water, 2.7 g) was added. A hydrogenation head was attached and the vessel was purged with nitrogen (3x), followed by hydrogen (3x). The vessel was left at 50 psi of hydrogen. After 1 hr of stirring, the reaction was complete by LCMS. The mixture was filtered through a Celite pad and concentrated to afford a black oil that was purified on silica gel (hexanes/ethyl acetate). Collected fractions gave the product as a clear oil (8.6 g, 62% yield).). ^{1}H NMR showed the desired compound.

[1000] **Part E.** The saturated alcohol from **Part D** (7.6 g, 30.0 mmol) was dissolved in dimethylsulfoxide (60 ml). Sodium hydride (Aldrich, 60 % in oil dispersion,

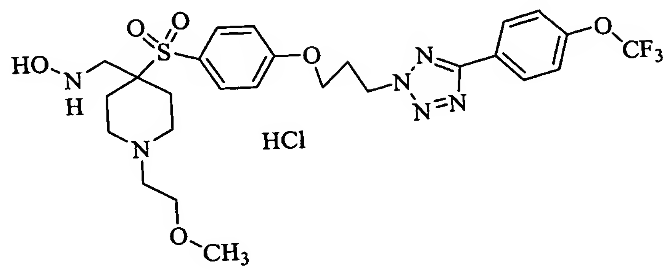
1.3 g, 32.6 mmol) was added portion wise over 30 min. After stirring for 1 hr, the aryl-fluoride, SC 84087, was added and the reaction was stirred overnight at ambient temperature. The reaction was quenched with saturated NH_4Cl_{aq} (100 ml) then extracted with ethyl acetate (3x-125 ml). The combined organics were washed with water (2x-200 ml) and brine (1x-200 ml) then dried over Na_2SO_4 filtered and concentrated to a brown oil. The residue was purified on silica gel (hexanes/ethyl acetate) to afford the product as a tan solid (14.0 g, 81% yield).). ^{1}H NMR showed the desired compound at 90% purity.

[1001] **Part F.** The *t*-butyl ester from **Part E** (9.5 g, 15.0 mmol) was dissolved in methylene chloride (30 ml) after which, trilfluoroacetic acid (Aldrich, 30 ml) was added. The reaction stirred for 4 hr then was concentrated to one-third volume via a nitrogen stream. The slightly viscous residue was then dripped into stirring diethyl ether to form a solid that was filtered and dried to give the product as a tan solid (6.9 g, 66 % yield).). ^{1}H NMR showed the desired compound.

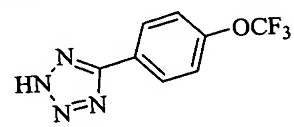
[1002] **Part G.** To a solution of the carboxylic acid of **Part F** (6.9 g, 9.9 mmol) in N,N-dimethylformamide (20 ml) was added triethylamine (Aldrich, 4.2 ml, 30.0 mmol) followed by N-hydroxybenzotriazole hydrate (Aldrich, 2.7 g, 20.0 mmol), O- (tetrahydro-2H-pyran-2-yl) hydroxylamine (2.34 g, 20.0 mmol), and, lastly, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 4.18 g, 21.8 mmol). The reaction stirred at room temperature for 18 hr. The mixture was diluted with water (30ml) then extracted with ethyl acetate (3x- 100 ml). The organics were combined and washed with saturated $NaHCO_{3\,aq}$ (3x-100 ml), water (2x- 100ml), and brine (1x- 150 ml). After drying over Na_2SO_4, the mixture was filtered and concentrated for a tan oil. The oil was tritiated with ethanol (3x) and methanol (3x) to afford a tan oil (8.1 g, 100^+ % yield). ^{1}H NMR showed the desired compound with trace impurities.

[1003] **Part H.** The crude protected hydroxamic acid of **Part G** (~ 9.9 mmol) was slurried in methanol (4 ml) and stirred with 4 N HCl in dioxane (20 ml) for 1 hr. The solvent volume was reduced in half then diethylether was added, providing a gummy solid that was purified by Reverse Phase LC (C_{18}, acetonitrile/water). The resulting partial TFA salt was dissolved in 4 N HCl in dioxane (20 ml) and stirred for 1 hr. The solvent volume was again reduced in half then diethyl ether was added, providing a white solid. The solid was collected and dried to afford the desired hydrochloride salt as a white powder (3.35g, 54% yield). ^{1}H NMR showed the desired compound.

[1004] **Example 48: Preparation of:**

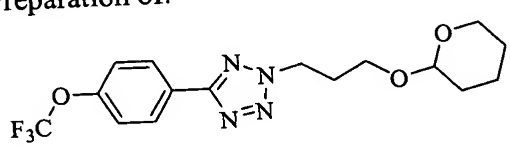


[1005] **Part A.** Preparation of:



A mixture of lithium chloride (1.71 g, 40.3 mmol), trifluoromethoxy-benzonitrile (5.00 g, 26.7 mmol), and sodium azide (1.75 g, 26.7 mmol) in 2-methoxyethanol (26 mL) under an N_2 atmosphere was refluxed for 4 hr. The ambient mixture was poured into a mixture of ice (84 g) and concentrated HCl (8.4 mL) and stirred until the ice melted. The white solid was collected by filtration, washed with water, and dried for 2 hr in a 40°C vacuum oven to produce the tetrazole in the form of an off white solid (4.86 g, 79% yield). MS MH^+ calcd. for $C_8H_6N_4OF_3$ 231, found 231.

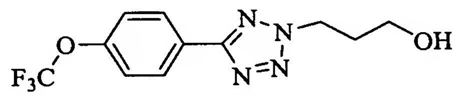
[1006] **Part B**. Preparation of:



A solution of the tetrazole of **Part A** (2.00 g, 8.69 mmol) in NMP (12 mL) was added dropwise to an ambient mixture of 95% sodium hydride (0.438 g, 18.2 mmol) in NMP (12 mL) under an N_2 atmosphere. After an 1 hr of stirring, 2-(3-chloropropoxy)tetrahydro-2H-pyran (1.58 mL, 9.56 mmol) was added dropwise. The mixture was stirred at ambient temperature for 18 hr and then at 70°C for 2 hr. The mixture was diluted with a solution of water (200 mL) and saturated $NaHCO_3$ (100 mL), and extracted with ethyl acetate (3x100 mL). The organic layer was washed with water (2x100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to produce a yellow liquid. Flash chromatography purification (ethyl acetate-hexane/silica gel) provided the pyran in the

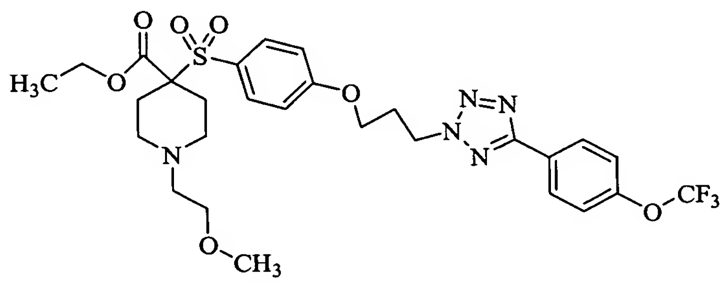
form of a white solid (1.46 g, 45% yield). Anal. Calcd. for $C_{16}H_{19}N_4O_3F_3$: C,56.34; H, 5.98; N, 7.73; S, 4.42. Found C,56.13; H, 6.08; N, 7.65; S, 4.75.

[1007] **Part C.** Preparation of:



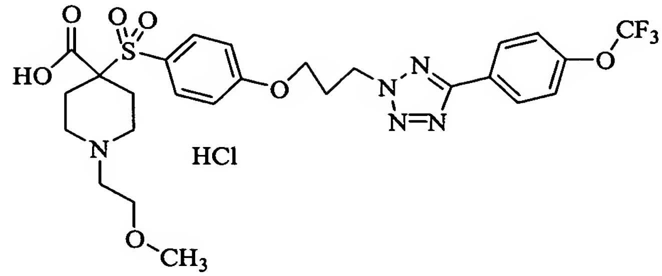
To an ambient solution of the pyran of **Part B** (1.40 g, 3.76 mmol) in MeOH (13.5 mL) was added a solution of acetyl chloride (0.896 mL, 13.1 mmol) in MeOH (13.5 mL). After 15 min, the solution was concentrated *in vacuo* to provide the alcohol in the form of a solid (1.02 g, 94% yield). MS MH^+ calcd. for $C_{11}H_{12}N_4O_2F_3$ 289, found 289.

[1008] **Part D.** Preparation of:



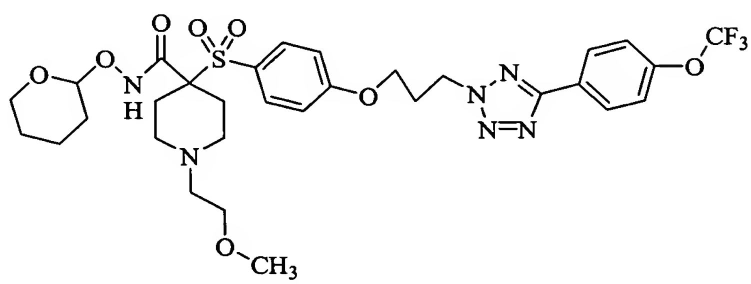
To an ambient mixture of 95% sodium hydride (0.110g, 3.58 mmol) in NMP (2.5 mL) under an N_2 atmosphere was added dropwise a solution of the alcohol of **Part C** (1.00 g, 3.47 mmol) in NMP (3.2 mL), and then the mixture was heated at 55°C for 30 min. A solution of ethyl 4-[(4-fluorophenyl)sulfonyl]-1-(2-methoxyethyl)piperidine-4-carboxylate (1.22 g, 3.27 mmol) in NMP (3.2 mL) was added dropwise to the 55°C reaction mixture. After 1 hr at 55°C, the ambient mixture was diluted with a solution of water (600 mL) and $NaHCO_3$ (100 mL), and extracted with ethyl acetate (3x200 mL). The organic layer was washed with water (2x150 mL) and brine (150 mL), dried over $MgSO_4$, and concentrated *in vacuo* to form a yellow oil (1.96 g). Flash chromatography purification (MeOH-EA/silica gel) provided the sulfone in the form of a yellow oil (1.48 g, 70% yield). MS MH^+ calcd. for $C_{28}H_{35}N_5O_7SF_3$ 642, found 642.

[1009] **Part E.** Preparation of:



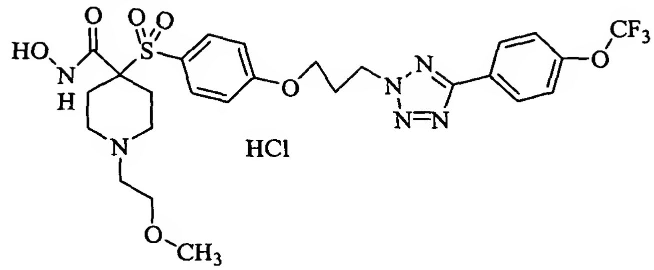
A mixture of the sulfone of **Part D** (1.44 g, 2.24 mmol) and 50% aqueous NaOH (1.08 g, 22.4 mmol) in a solution of THF (23 mL) and EtOH (11 mL) was stirred at ambient temperature for 3 hr and then 60°C for 15 min. The mixture was concentrated *in vacuo*, diluted with a solution of acetonitrile and water, acidified to a pH of approximately 2 with concentrated HCl, and concentrated *in vacuo* to provide the acid (containing NaCl) as a crude tan foam (2.77 g). MS MH^+ calcd. for $C_{26}H_{31}N_5O_7SF_3$ 614, found 614.

[1010] **Part F.** Preparation of:



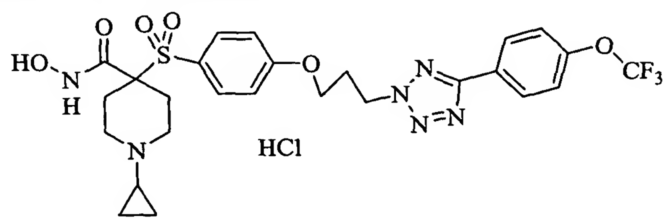
A mixture of the crude acid of **Part E** (2.24 mmol), 1-hydroybenzotriazole hydrate (0,534 g, 3.95 mmol), triethylamine (3.62mL, 25.9 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.542 g, 4.63 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.888 g, 4.63 mmol) in DMF (23 mL) under an N_2 atmosphere was stirred at ambient temperature for 40 hr. The mixture was diluted with water (400 mL) and extracted with ethyl acetate (3x100 mL). The organic layer was washed with water (2x100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to form a white foam (1.37 g). Chromatography purification (MeOH-EA/silica gel) produced the O-protected hydroxamate in the form of a white foam (1.04 g, 65% based on the ester of Part 1D). MS MH^+ calcd. for $C_{31}H_{40}N_6O_8F_3S$ 713, found 713. Anal. Calcd. for $C_{31}H_{39}N_6O_8F_3S$: C,52.24; H, 5.52; N,11.79. Found C,52.47; H, 5.73; N, 11.64.

[1011] **Part G.** Preparation of:

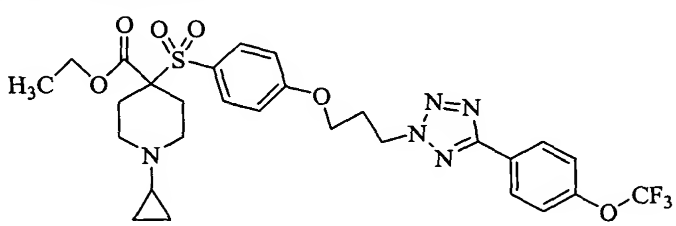


A solution of the O-protected hydroxamate of **Part F** (0.960 g, 1.35 mmol) and acetyl chloride (0.493 g, 6.53 mmol) in methanol (15 mL) was stirred at ambient temperature for 1 hr. The solution was concentrated *in vacuo* to a white solid. The solid was triturated with ether and concentrated *in vacuo* to provide the title compound in the form of a white solid (0.66 g, 74% yield). Anal. Calcd. for $C_{26}H_{31}N_6O_7F_3S{\cdot}HCl$: C, 46.95; H, 4.85; N, 12.64; Cl, 5.33; S, 4.82. Found C, 46.59; H, 5.07; N, 12.64; Cl, 5.36; S, 5.20. MS MH^+ calcd. for $C_{26}H_{32}N_6O_7F_3S$ 629, found 629.

[1012] **Example 49. Preparation of:**



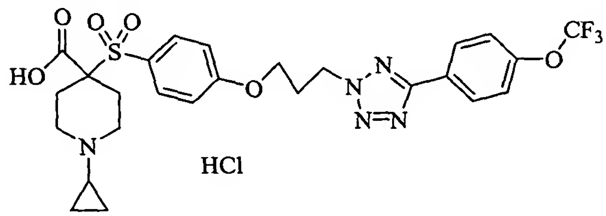
[1013] **Part A.** Preparation of:



To an ambient mixture of 95% sodium hydride (0.397g, 16.5 mmol) in NMP (7 mL) under an N_2 atmosphere was added dropwise a solution of the alcohol of **Part C of Example 48** (3.44 g, 11.9 mmol) in NMP (7 mL). The mixture was then stirred at ambient temperature for 45 min. The ethyl 1-cyclopropyl-4-[(4-fluorophenyl)sulfonyl]piperidine-4-carboxylate (4.00 g, 11.3 mmol) was added in one portion, and the mixture was heated to 60°C. After heating for 24 hr at 60°C and adding 2 more portions of 95% sodium hydride (0.10 g, 4.0

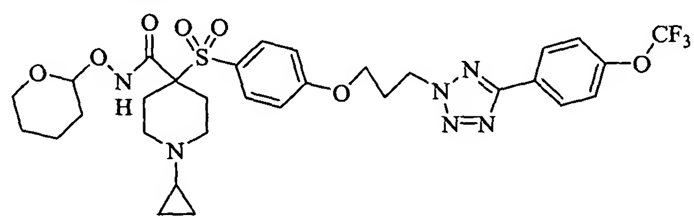
mmol and 0.08 g, 3.0 mmol), the mixture was diluted with water (300 mL) and extracted with ethyl acetate (3x100 mL). The organic layer was washed with water (2x100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to form a yellow oil (5.81 g). Flash chromatography purification (Hexane-EA/silica gel) produced the sulfone in the form of a yellow oil (3.10 g, 44% yield). The proton NMR ($CDCl_3$) spectrum was consistent with the desired sulfone product.

[1014] **Part B.** Preparation of:



A mixture of the sulfone of **Part A** (3.00 g, 4.81 mmol) and 50% aqueous NaOH (3.85 g, 48.1 mmol) in a solution of THF (50 mL) and EtOH (24 mL) was stirred for 2.5 hr at 60°C. The mixture was concentrated *in vacuo*, diluted with a solution of acetonitrile and water, acidified to a pH of approximately 2 with concentrated HCl, and concentrated *in vacuo*. The crude acid was purified by reverse phase HPLC (H_2O-CH_3CN) to produce the acid in the form of a white solid (1.86 g, 55% yield). MS MH^+ calcd. for $C_{26}H_{29}N_5O_6F_3S$ 596, found 596.

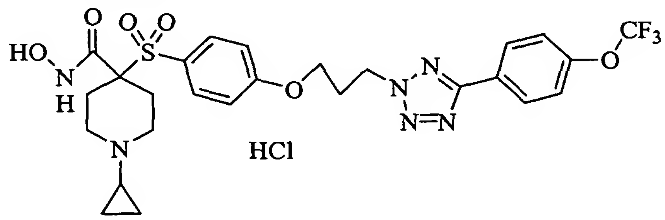
[1015] **Part C.** Preparation of:



A mixture of the acid of **Part B** (1.80 g, 2.85 mmol), 1-hydroybenzotriazole hydrate (0.679 g, 5.02 mmol), triethylamine (4.61mL, 33.1 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.692 g, 5.91 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.13 g, 5.91 mmol) in DMF (29 mL) under an N_2 atmosphere was stirred at ambient temperature for 24 hr and 57°C for 6.5 hr. The mixture was concentrated *in vacuo*, diluted with water (300 mL), and extracted with ethyl acetate (3x100 mL). The organic layer was washed with water (2x100 mL) and brine (100 mL),

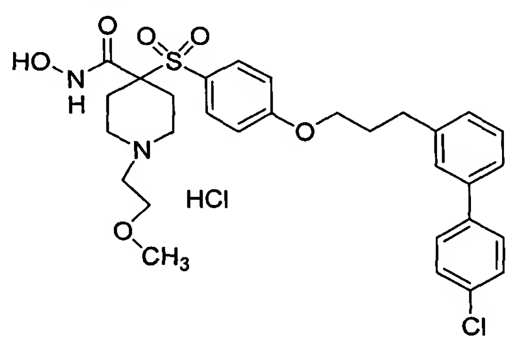
dried over $MgSO_4$, and concentrated *in vacuo* to form a yellow oil (1.80 g). Flash chromatography purification ($MeOH-CH_2Cl_2$/silica gel) produced the O-protected hydroxamate in the form of a white foam (0.89 g, 45% yield). MS MH^+ calcd. for $C_{31}H_{38}N_6O_7F_3S$ 695, found 695. Anal. Calcd. for $C_{31}H_{37}N_6O_7F_3S$: C,53.59; H, 5.37; N,12.10; S, 4.62. Found C,53.30; H, 5.43; N, 12.05; S, 4.73.

[1016] **Part D.** Preparation of:

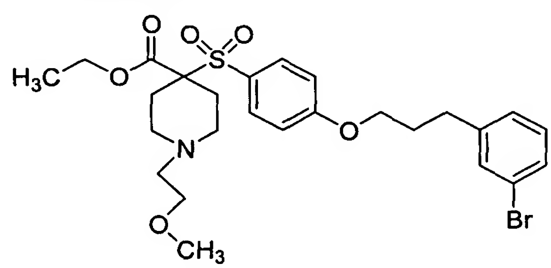


A solution of the O-protected hydroxamate of **Part C** (0.870 g, 1.25 mmol) and acetyl chloride (0.456 g, 6.04 mmol) in methanol (14 mL) was stirred at ambient temperature for 30 min. The mixture was poured into diethyl ether (250 mL). The white solid was isolate by filtration and dried in a 40°C vacuum oven to produce the title compound in the form of a white solid (0.56 g, 69% yield). MS MH^+ calcd. for $C_{26}H_{30}N_6O_6F_3S$ 611, found 611.

[1017] **Example 50. Preparation of:**

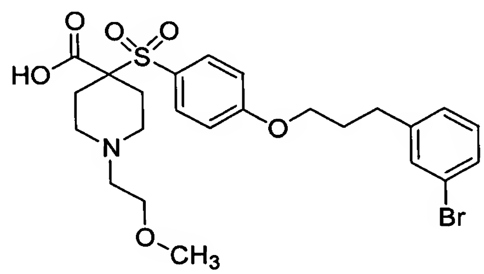


[1018] **Part A.** Preparation of:



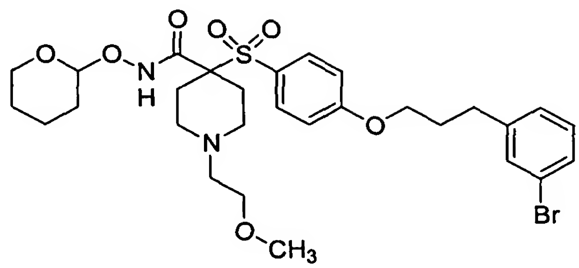
To a solution of the alcohol from **Part B of Example 38** (3.65 g, 17.0 mmol) in anhydrous dimethylformamide (17 mL) at 5°C was added 60% sodium hydride (0.77 g, 19.3 mmol) in portions. After completion of the addition, the reaction was stirred at 5°C for 15 min and then at ambient temperature for 15 min. The reaction was cooled to 5°C and ethyl 4-[(4-fluorophenyl)sulfonyl]-1-(2-methoxyethyl)piperidine-4-carboxylate (6.0 g, 16.1 mmol) in anhydrous dimethylformamide (15 mL) was added slowly. Reaction stirred at room temperature for 2 hr, then was diluted with water (250 mL) and extracted with ethyl acetate (3x150 mL). The combined organics were washed with brine and dried over magnesium sulfate. Silica Gel chromatography (ethyl acetate/hexane) gave the product as a colorless oil (8.06 g, 88%). NMR($CDCl_3$) δ 1.20-1.26 (m, 3H), 1.88-2.02 (m, 2H), 2.06-2.27 (m, 4H), 2.43 (d, 2H), 2,53 (bs, 2H), 2.78 (t, 2H), 2.97-3.08 (m, 2H), 3.32 (s, 3H), 3.47 (bs, 2H), 4.00 (t, 2H), 4.18 (q, 2H), 6.95 (d, 2H), 709-7.18 (m, 2H), 7.34 (d, 2H), 7.68 (d, 2H).

[1019] **Part B.** Preparation of:



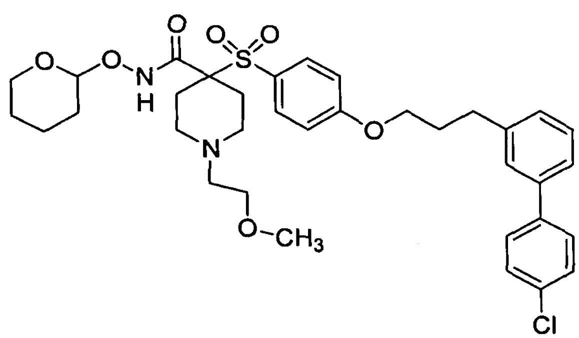
The impure ester of **Part A** (8.06 g, 14.2 mmol theoretical) was hydrolyzed in 15 mL of ethanol, 15 mL of 1,4-dioxane and 9.5 mL of 6 N NaOH at 60°C. The solution was poured into water and extracted with ether to remove color. Acidification with 1N HCl caused precipitation of the acid which was collected by filtration and washed with water and hexane then dried under high vacuum yielding the acid as an off white solid (5.90 g, 76.8 % yield). NMR (CD_3OD w/ K_2CO_3) δ 2.00 (q, 2H), 2.07-2.19 (m, 4H), 2.32 (d, 2H), 2.48 (t, 2H), 2.79 (d, 2H), 2.91 (d, 2H), 3.45 (t, 2H), 4.06 (t, 2H), 7.04 (d, 2H), 7.20 (d, 2H), 7.29-7.35 (m, 1H), 7.40 (s, 1H), 7.78 (d, 2H).

[1020] **Part C.** Preparation of:



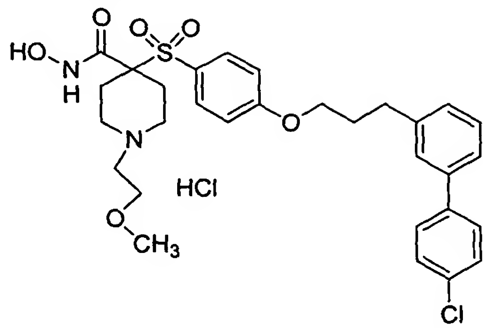
To the acid of **Part B** (5.90, 10.9 mmol), EDC (2.9 g, 15.3 mmol), and HOBt (2.5g, 16.4 mmol) in anhydrous NMP (33 mL) was added triethylamine (4.5 mL, 32.7 mmol). After heating at 60°C for 1 hr, THP-hydroxylamine (1.9 g, 16.4 mmol) was added. The solution was stirred for 18 hr at 60°C, additional EDC (2.9 g, 15.3 mmol), HOBt (2.5g, 16.4 mmol), triethylamine (4.5 mL, 32.7 mmol) and THP-hydroxylamine (1.9 g, 16.4 mmol) were added. After 2 hr, the reaction was diluted with water (300 mL) and extracted with ethyl acetate (3x150 mL). The combined organics were washed with brine and dried over magnesium sulfate. Silica gel Chromatography (ethyl acetate/hexanes) provided the protected hydroxamate as a viscous impure colorless oil (5.70 g). ESMS *m/z* = 641 $(M+H)^+$.

[1021] **Part D.** Preparation of:



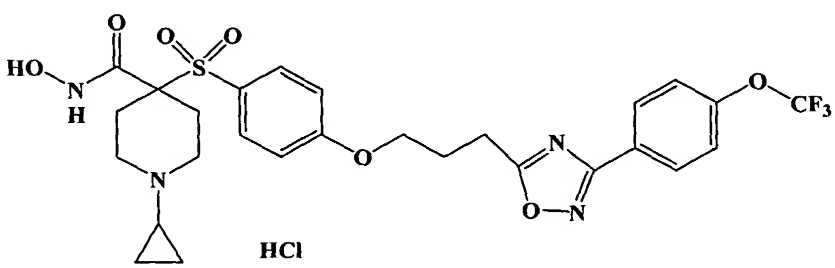
In a vial were combined the aryl bromide from **Part C** (0.50 g, 0.78 mmol) in 3 mL of dimethoxyethyl ether, 4-chlorobenzeneboronic acid (185 mg, 1.17 mmol), palladium tetrakistriphenylphosphine (~45 mg, 0.04 mmol) and 2M cesium carbonate (1.17 mL, 2.34 mmol). Mixture stirred vigorously at 80°C for 18 hr. Reaction poured onto 2 mL Chem-Elut tube prewetted with 3 mL of water and eluted with ethyl acetate and methylene chloride. Purification by reverse phase chromatography (acetonitrile/water/0.05% TFA) gave the TFA salt of the deprotected material (239.6 mg) which was carried on as is.

[1022] **Part E.** Preparation of:



The product from **Part D** (239.6 mg) was taken up in 4M hydrochloric acid in 1,4-dioxane (2 mL) and methanol (1-2 mL) and stirred for 0.5 hr then concentrated. This was repeated. Product crashed out of solution, was collected by filtration, washed with diethyl ether and dried under high vacuum yielding the title compound as colorless solid (170.5 mg, 35% over two steps). ESMS $m/z = 587\ (M+H)^+$. HRMS calcd. for $C_{30}H_{36}ClN_2O_6S$: 587.1977 $(M+H)^+$. Found: 587.1979.

[1023] **Example 51. Preparation of 1-cyclopropyl-N-hydroxy-4-{[4-(3-{3-[4-(trifluoromethoxy) phenyl]-1,2,4-oxadiazol-5-yl}propoxy)phenyl]sulfonyl}piperidine-4-carboxamide hydrochloride.**



[1024] **Part A.** In dry equipment under nitrogen, potassium trimethylsilanolate (35.9 g, 0.28 mol) was dissolved in dimethylsulfoxide (250 mL) and gamma-butyrolactone (16.14 mL, 0.21 mol) was added over 10 min while the reaction temperature rose to 38°C. After stirring at ambient temperature for 40 min, sodium hydride (8.4 g of a 60% oil dispersion, 0.21 mol) was added portion wise over 20 min and the reaction temperature rose to 43°C. Gas evolution was also observed. After stirring at ambient temperature for 50 min, a solution of ethyl 1-cyclopropyl-4-[(4-fluorophenyl)sulfonyl]-4-piperidinecarboxylate (49.7g, 0.14 mol) in dimethylsulfoxide (50 mL) was added over 10

min as the reaction temperature rose to 38°C. The reaction was stirred at ambient temperature for 30 min. The slurry was slowly poured into ice water (1.5 L) and then extracted with hexanes (150 mL) 3 times followed by a diethyl ether extraction (300 mL). The aqueous layer was chilled to 5°C and the pH adjusted to 6 with concentrated hydrochloric acid. The slurry was filtered and the cake washed with 500 mL water two times. The solid was dried *in vacuo* to give the butyric acid as a white solid (47.5 g, 77%). LCMS m/z = 440 $[M+H]^+$.

[1025] **Part B.** In dry equipment under nitrogen, the butyric acid from **Part A** (3.07 g, 7.0 mmol) was dissolved in dry dimethylacetamide (15 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (1.42 g, 10.5 mmol), triethylamine (1.95 mL, 14.0 mmol), 4-(trifluoromethoxy)benzamidoxime (2.31 g, 10.5 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.68 g, 14.0 mmol). Additional dry dimethylacetamide (5 mL) was added. After 24 hr at 70°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/methanol/hexanes) provided the oxadiazole as a light white solid (3.38 g, 78%). LCMS m/z = 624$[M+H]^+$.

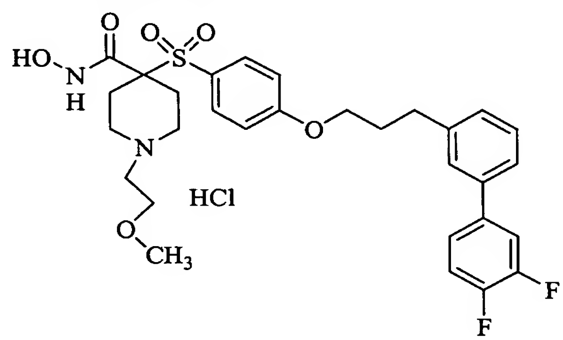
[1026] **Part C.** A slurry of the oxadiazole from **Part B** (3.36 g, 5.39 mmol), 2.5N sodium hydroxide (6.5 mL, 16.2 mmol) and sodium hydroxide (0.86 g, 21.6 mmol) in isopropanol (27 mL) was stirred at 75°C for 5 hr. The heat was removed and the reaction diluted with water (50 mL) and chilled to5°C. The pH was adjusted to 7 with concentrated hydrochloric acid. The solids were filtered, washed with hexanes, and dried *in vacuo* to give the carboxylic acid as a white solid (3.1 g, 97%). LCMS m/z = 596 $[M+H]^+$.

[1027] **Part D.** In dry equipment under nitrogen, the carboxylic acid from **Part C** (2.9 g, 4.87 mmol) was dissolved in dry dimethylacetamide (10 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (0.99 g, 7.3 mmol), triethylamine (2.03 mL, 14.6 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.86 g, 7.31 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.87 g, 9.75 mmol). Additional dry dimethylacetamide (5 mL) was added. After 29 hr at 40°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated $NaHCO_3$, saturated

sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/methanol/hexanes) provided the THP hydroxamate as a white foam (1.48 g, 44%). LCMS $m/z = 695$ $[M+H]^+$.

[1028] **Part E.** To the THP hydroxamate from **Part D** (1.4 g, 2.02 mmol) was added 4N HCl dioxane solution (5 mL, 20.2 mmol) and methanol (0.5 mL). The slurry became very thick. Diethyl ether (50 mL) was added to and after 1 hr at ambient temperature the reaction was filtered under nitrogen. The solids were washed with diethyl ether (150 mL) under nitrogen and dried *in vacuo* over phosphorus pentoxide to give the title compound as a white solid (1.4 g, 100%). HRMS (ES+) $M+H^+$ calculated for $C_{27}H_{29}N_4O_7S_1F_3$ 611.1787, found 611.1773.

[1029] **Example 52. Preparation of:**

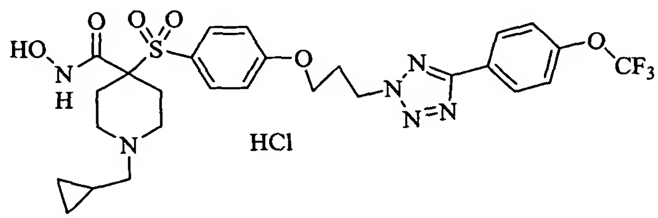


[1030] **Part A.** In a vial were combined the aryl bromide from **Part C of Example 50** (0.50 g, 0.78 mmol) in 3 mL of dimethoxyethyl ether, 3,4-difluorobenzeneboronic acid (185 mg, 1.17 mmol), palladium tetrakistriphenylphosphine (~45 mg, 0.04 mmol) and 2M cesium carbonate (1.17 mL, 2.34 mmol). Mixture stirred vigorously at 80°C for 18 hr. Reaction poured onto 2 mL Chem-Elut tube prewetted with 3 mL of water and eluted with ethyl acetate and methylene chloride. Purification by reverse phase chromatography (acetonitrile/water/0.05% TFA) gave the TFA salt of the deprotected material (354.8 mg) which was carried on as is.

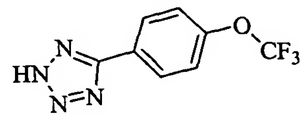
[1031] **Part B.** The product from **Part D** (354.8 mg) was taken up in 4M hydrochloric acid in 1,4-dioxane (2 mL) and methanol (1-2 mL) and stirred for 30 min and then concentrated. This was repeated. Product crashed out of solution, was collected by filtration, washed with diethyl ether and dried under high vacuum yielding the title

compound as a colorless solid (298.0 mg, 61% over two steps). ESMS *m/z* = 589 $(M+H)^+$. HRMS calcd. for $C_{30}H_{35}F_2N_2O_6S$: 589.2178 $(M+H)^+$. Found: 589.2192.

[1032] **Example 53. Preparation of:**

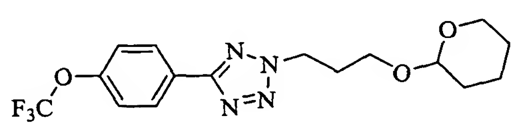


[1033] **Part A.** Preparation of:



A mixture of lithium chloride (1.71 g, 40.3 mmol), trifluoromethoxy-benzonitrile(5.00 g, 26.7 mmol), and sodium azide(1.75 g, 26.7 mmol) in 2-methoxyethanol(26 mL) under an N_2 atmosphere was refluxed for 4 hr. The ambient mixture was poured into a mixture of ice (84 g) and concentrated hydrochloric acid (8.4 mL), and then stirred until the ice melted. The resulting white solid was collected by filtration, washed with water, and dried for 2 hr in a 40°C vacuum oven to provide the tetrazole in the form of an off white solid (4.86 g, 79% yield). MS MH^+ calcd. for $C_8H_6N_4OF_3$ 231, found 231.

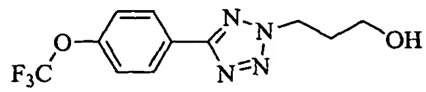
[1034] **Part B.** Preparation of:



A solution of the tetrazole of **Part A** (2.00 g, 8.69 mmol) in NMP (12 mL) was added dropwise to an ambient mixture of 95% sodium hydride (0.438 g, 18.2 mmol) in NMP (12 mL) under an N_2 atmosphere. After an 1 hr of stirring, 2-(3-chloropropoxy)tetrahydro-2H-pyran(1.58 mL, 9.56 mmol) was added dropwise. The mixture was stirred at ambient temperature for 18 hr and then at 70°C for 2 hr. The mixture was diluted with a solution of water (200 mL) and saturated $NaHCO_3$ (100 mL), and extracted with ethyl acetate (3x100 mL). The organic layer was washed with water (2x100 mL) and brine(100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow liquid. Flash chromatography purification (ethyl acetate-hexane/silica gel) provided the pyran in the

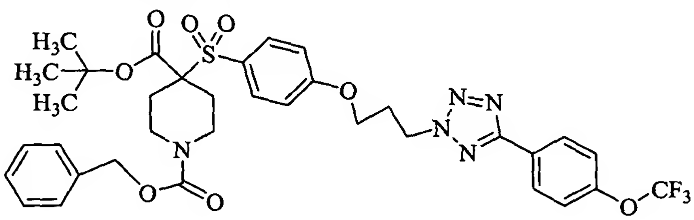
form of a white solid (1.46 g, 45% yield). Anal. Calcd. for $C_{16}H_{19}N_4O_3F_3$: C,56.34; H, 5.98; N, 7.73; S, 4.42. Found C,56.13; H, 6.08; N, 7.65; S, 4.75.

[1035] **Part C.** Preparation of:



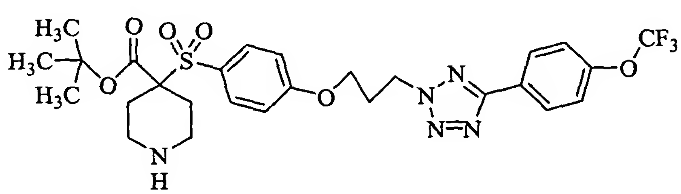
To an ambient solution of the pyran of **Part B** (1.40 g, 3.76 mmol) in MeOH (13.5 mL) was added a solution of acetyl chloride (0.896 mL, 13.1 mmol) in MeOH (13.5 mL). After 15 min, the solution was concentrated *in vacuo* to provide the alcohol in the form of a solid (1.02 g, 94% yield). MS MH^+ calcd. for $C_{11}H_{12}N_4O_2F_3$ 289, found 289.

[1036] **Part D.** Preparation of:



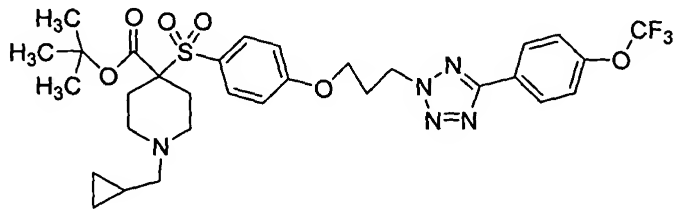
To an ambient mixture of 95% sodium hydride (0.923g, 38.5 mmol) in NMP (16 mL) under an N_2 atmosphere was added dropwise a solution of the alcohol of **Part C** (8.00 g, 27.7 mmol) in NMP(16 mL), and the mixture was stirred at ambient temperture for 35 minutes. A solution of 1-benzyl 4-tert-butyl 4-[(4-fluorophenyl)sulfonyl]piperidine-1,4-dicarboxylate (12.5 g, 26.3 mmol) in NMP (16 mL) was added dropwise to the reaction mixture. After 3 hr at 55°C, the ambient mixture was diluted with water (700 mL) and extracted with ethyl acetate (3x150 mL). The organic layer was washed with water (2x100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to produce a yellow oil (18.6 g). Chromatography purification (hexane-EA/silica gel) provided the sulfone as a yellow oil (10.1 g, 52% yield). MS MH^+ calcd. for $C_{35}H_{39}N_5O_8SF_3$ 746, found 746. Anal. Calcd. for $C_{35}H_{38}N_5O_8SF_3$ C,56.37; H, 5.14; N, 9.39; S, 4.30. Found C,56.22; H, 4.96; N, 9.22; S, 4.37.

[1037] **Part E.** Preparation of:



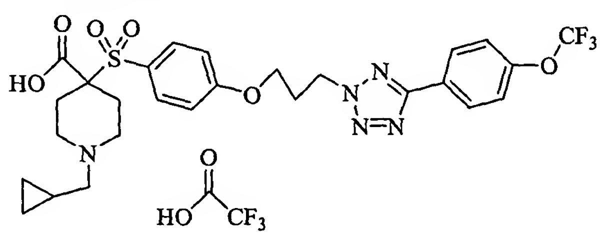
A mixture of the sulfone of **Part D** (10.0 g, 13.4 mmol) and 10% palladium on carbon (1.43g, 1.34 mmol) in methanol (50 mL) was placed under an H_2 atmosphere with a balloon at ambient temperature for 20 hr. The mixture was filtered through a bed of celite and concentrated *in vacuo* to provide the piperidine in the form of a pale yellow oil (7.57 g, 92%). The proton NMR spectrum was consistent for the desired compound.

[1038] **Part F.** Preparation of:



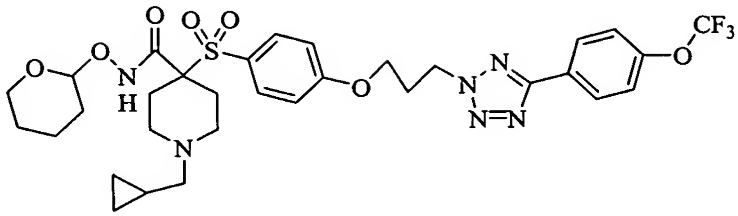
A mixture of the piperidine of **Part E** (3.50 g, 5.72 mmol), (bromomethyl)cyclopropane (0.67 mL,6.87 mmol), and potassium carbonate (2.38 g, 17.2 mmol) in DMF (15 mL) was stirred at ambient temperature for 20 hr under an N_2 atmosphere. The mixture was diluted with water (700 mL) and extracted with ethyl acetate (3x100 mL). The organic layer was washed with water (2x75 mL) and brine (75 mL), dried over $MgSO_4$, and concentrated *in vacuo* to produce a yellow oil. Flash chromatography purification (hexane-EA/silica gel) provided the alkylpiperidine in the form of a colorless oil(2.08 g, 55% yield): MS MH^+ calcd. for $C_{31}H_{39}N_5O_6SF_3$ 666, found 666. Anal. Calcd. for $C_{31}H_{38}N_5O_6SF_3$: C,55.93; H, 5.75; N, 10.52; S, 4.82. Found C,55.85; H, 5.91; N, 10.25; S, 4.99.

[1039] **Part G.** Preparation of:



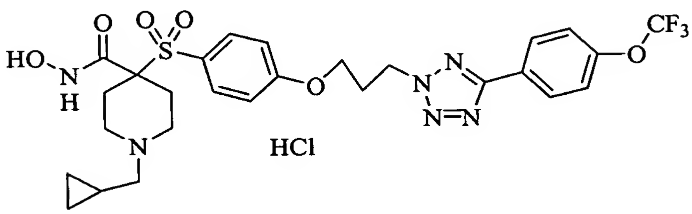
A solution of the alkylpiperidine of **Part F** (2.00 g, 3.00 mmol) in trifluoroacetic acid (10 mL, 130 mmol) was stirred at ambient temperature for 1.7 hr. The mixture was concentrated *in vacuo*, triturated twice with ether, and dried in a 40°C vacuum to provide the acid as a white solid (2.21 g, 102%). MS MH^+ calcd. for $C_{27}H_{31}N_5O_6SF_3$ 610, found 610.

[1040] **Part H.** Preparation of:



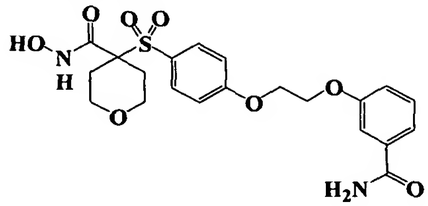
A mixture of the crude acid of **Part G** (2.10 g, 3.44 mmol), 1-hydroybenzotriazole hydrate(0.820 g, 6.07 mmol), triethylamine(5.57mL, 39.9 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine(0.835 g, 7.13mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.37 g, 7.13 mmol) in DMF (35 mL) under an N_2 atmosphere was stirred at ambient temperature for 20 hr. The mixture was diluted with water (700 mL) and extracted with ethyl acetate (3x200 mL). The organic layer was washed with water (2x100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to produce a yellow foam. Chromatography purification (MeOH-CH_2Cl_2/silica gel) produced the O-protected hydroxamate in the form of a white foam (1.60 g, 66%). MS MH^+ calcd. for $C_{32}H_{40}N_6O_7F_3S$ 709, found 709.

[1041] **Part I.** Preparation of:

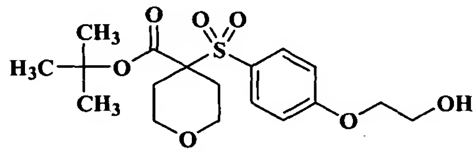


A solution of the O-protected hydroxamate of **Part H** (1.50 g, 2.12 mmol) and acetyl chloride(0.677 mL, 10.2 mmol) in methanol (23 mL) was stirred at ambient temperature for 1 hr. The solution was diluted with ether and a solid formed. The solid was isolated by filtration, washed with ether, and dried in a 40°C vacuum oven to produce the title compound as a white solid (1.55 g, 82% yield). Anal. Calcd. for $C_{27}H_{31}N_6O_6F_3S \cdot HCl$: C, 49.05; H, 4.88; N, 12.71; Cl, 5.36; S, 4.85. Found C, 48.94; H, 4.72; N, 12.71; Cl, 5.29; S, 4.94

[1042] **Example 54. Preparation of:**

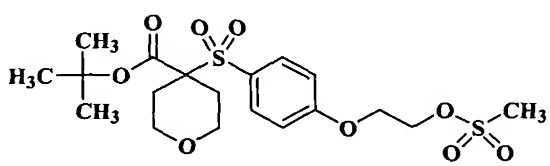


[1043] **Part A.** Preparation of:



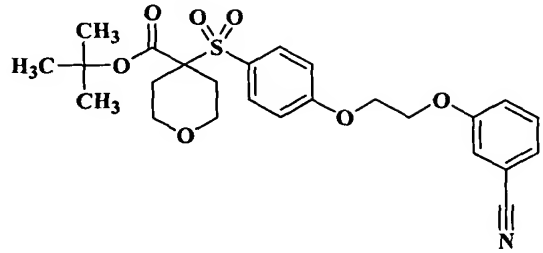
To a solution of tert-butyl 4-[(4-fluorophenyl)sulfonyl]tetrahydro-2H-pyran-4-carboxylate (5.0 g, 14.6 mmol) and cesium carbonate (14.3 g, 43.8 mmol) in anhydrous DMSO (30 mL) was added ethylene glycol (8.1 mL, 146 mmol). The resulting reaction mixture was stirred at 80°C for 3 hr. After cooling to room temperature, the mixture was poured into water (350 mL) and extracted with ethyl acetate (3x). The organics were washed with brine and dried over magnesium sulfate. Silica gel chromatography (ethyl acetate/methylene chloride) provided the alcohol as a colorless solid (2.33 g, 41%). NMR($CDCl_3$) δ 1.45 (s, 9H), 2.13-2.20 (m, 4H), 3.22-3.33 (m, 2H), 3.94-4.03 (m, 4H), 4.16 (q, 2H), 7.02 (d, 2H), 7.73 (d, 2H). ESMS $m/z = 404$ (M+NH4)$^+$. HRMS calcd. for $C_{18}H_{26}O_7S$ NH_4: 404.1743 (M+NH_4)$^+$. Found: 404.1734.

[1044] **Part B.** Preparation of:



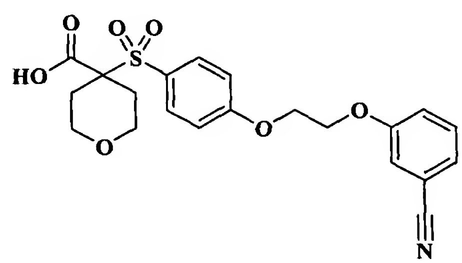
To a solution of the alcohol from **Part A** (0.50 g, 1.3 mmol) in CH_2Cl_2 (2.5 mL) was added triethylamine (0.24 mL g, 1.7 mmol), followed by mesyl chloride. The resulting mixture was stirred at room temperature for 1.5 hr. The mixture was diluted with methylene chloride and washed with 10% citric acid, washed with 5% sodium bicarbonate, washed with brine, and dried over $MgSO_4$. Concentration produced the desired compound in the form of a tan solid (0.62 g, 100%). NMR($CDCl_3$) 1.45 (s, 9H), 2.13-2.22 (m, 4H), 3.07 (s, 3H), 3.22-3.37 (m, 2H), 4.00 (dt, 2H), 4.32-4.37 (m, 2H), 4.58-4.62 (m, 2H), 7.02 (d, 2H), 7.75 (d, 2H). ESMS $m/z = 482$ (M+NH4)$^+$.

[1045] **Part C.** Preparation of:



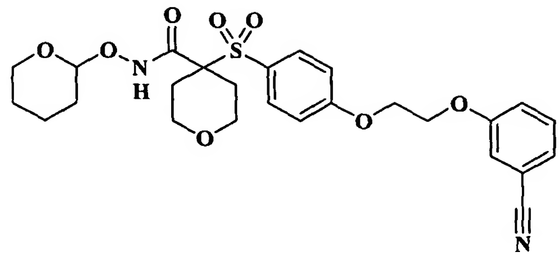
To a solution of 60% sodium hydride (39 mg, 0.98 mmol) in anhydrous dimethylformamide (2.5 mL) was added 3-cyanophenol (108 mg, 0.91 mmol). After stirring for 15 min, solution was clear. The mesylate from **Part B** (0.30 g, 0.65 mmol) in anhydrous dimethylformamide (1 mL) was added. After completion of the addition, the mixture as stirred at ambient temperature overnight. The next morning, the mixture was poured onto a 10 mL Chem-Elut tube, prewetted with 5 mL of water, and eluted with ethyl acetate and CH_2Cl_2. Chromatography (silica gel with ethyl acetate/hexane) produced the desired ester (0.27 g, 85%). NMR ($CDCl_3$) δ1.46 (s, 9H), 2.17-2.21 (m, 4H), 3.22-3.36 (m, 2H), 3.98 (dt, 2H), 4.35-4.43 (m, 4H), 7.04 (d, 2H), 7.15-7.20 (m, 2H), 7.28 (dt, 1H), 7.39 (t, 1H), 7.74 (d, 2H). ESMS *m/z* = 505 (M+NH4)$^+$. HRMS calcd. for $C_{25}H_{33}N_2O_7S$: 505.2008 (M+NH_4)$^+$. Found: 505.2019.

[1046] **Part D.** Preparation of:



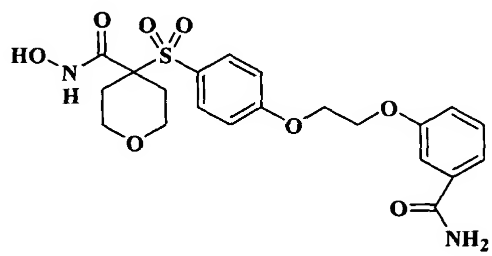
The ester of **Part C** (0.24 g, 0.49 mmol) was hydrolyzed in 5 mL of methylene chloride and 5 mL of trifluoroacetic acid. Concentration and drying under high vacuum produced the desired acid (0.21 g, 100%). NMR (CD_3OD w/ K_2CO_3) δ 2.01-2.11 (m, 2H), 2.20 (d, 2H), 3.32-3.42 (m, 2H), 3.95 (dt, 2H), 4.38-4.45 (m, 4H), 7.13 (d, 2H), 7.26-7.34 (m, 3H), 7.45 (t, 1H), 7.76 (d, 2H). ESMS *m/z* = 449 (M+NH4)$^+$. HRMS calcd. for $C_{21}H_{21}NO_7S$ NH_4: 449.1382 (M+NH_4)$^+$. Found: 449.1407.

[1047] **Part E.** Preparation of:



To a slurry of the acid of **Part D** (0.20 g, 0.46 mmol), HOBt (76 mg, 0.55 mmol), and EDC (130 mg, 0.68 mmol) was added triethylamine (1.4 mmol) and THP-hydroxylamine (167 mg, 1.4 mmol) in a flask under N_2 in 2 mL anhydrous DMF. The resulting mixture was stirred at 40°C overnight. The next morning, the mixture was poured onto 10 mL Chem-Elut tube prewetted with 6 mL of water and eluted with ethyl acetate and CH_2Cl_2. Chromatography (silica gel, ethyl acetate/hexane) produced the product as a colorless oil (0.18 g, 74%).

[1048] **Part F.** Preparation of:



To the product from **Part E** (0.18 g, 0.34 mmol) in methanol (1-2 mL) was added 4M HCl in 1,4-dioxane (2.5 mL). The resulting mixture was stirred overnight. Reverse phase chromatography (water/acetonitrile/0.05% TFA) produced the desired compound as a colorless crystalline solid (25.0 mg 16 %). NMR(DMSO) δ 1.82-1.98 (m, 2H).2.15-2.30 (m, 2H), 3.15, (t, 2H), 3.86 (d, 2H), 4.44 (d, 4H), 7.10-7.25 (m, 3H), 7.38 (t, 1H), 7.44-7.52 (m, 2H), 7.68 (d, 2H).ESMS $m/z = 465\ (M+H)^+$. HRMS calcd. for $C_{21}H_{25}N_2O_8S$: 465.1332 $(M+H)^+$. Found: 465.1354.

[1049] **Examples 55-89. *In Vitro* MMP Inhibition Analysis**

[1050] Several hydroxamates and salts thereof were analyzed in *in vitro* assays to determine their ability to inhibit the MMP cleavage of peptide substrates. Inhibition (K_i) and IC_{50} constants were calculated from the assayed hydroxamate-MMP interactions.

[1051] Human recombinant MMP-1, MMP-2, MMP-9, MMP-13, and MMP-14 were used in this assay. All enzymes were prepared in Assignee's laboratories following usual laboratory procedures. Protocols for the preparation and use of these enzymes are available in the scientific literature. *See, e.g., Enzyme Nomenclature* (Academic Press, San Diego, CA, 1992) (and the citations therein). *See also*, Frije et al., *J Biol. Chem.*, 26(24), 16766-73 (1994).

[1052] The MMP-1 proenzyme was purified from the spent media of MMP-1-transfected HT-1080 cells provided by Dr. Harold Welgus of Washington University (St. Louis, MO). The protein was purified on a zinc chelating column.

[1053] The MMP-2 proenzyme was purified by gelatin Sepharose chromatography from MMP-2- transfected p2AHT2 cells provided by Dr. Gregory Goldberg of Washington University (St. Louis, MO).

[1054] The MMP-9 proenzyme was purified by gelatin Sepharose chromatography from spent media of MMP-9- transfected HT1080 cells provided by Dr. Howard Welgus of Washington University (St. Louis, MO).

[1055] The MMP-13 was obtained as a proenzyme from a full-length cDNA clone using baculovirus, as described by V.A. Luckow, "Insect Cell Expression Technology," *Protein Engineering: Principles and Practice,* pp. 183-218 (edited by J.L. Cleland et al., Wiley-Liss, Inc., 1996). The expressed proenzyme was first purified over a heparin agarose column, and then over a chelating zinc chloride column. The proenzyme was then activated by APMA for use in the assay. Further details on baculovirus expression systems may be found in, for example, Luckow et al., *J. Virol.*, 67, 4566-79 (1993). *See also*, O'Reilly et al, *Baculovirus Expression Vectors: A Laboratory Manual* (W.H. Freeman and Co., New York, NY, 1992). *See also*, King et al., *The Baculovirus Expression System: A Laboratory Guide* (Chapman & Hall, London, England, 1992).

[1056] The MMP-14 full length cDNA was provided by Dr. Gregory Goldberg of Washington University (St. Louis, MO). The catalytic domain enzyme was expressed in *E. coli* inclusion bodies, solubilized in urea, purified on a preparative C-14 reverse phase HPLC column, and then refolded in the presence of zinc acetate and purified for use.

[1057] All MMPs were activated using 4-aminophenylmercuric acetate ("APMA", Sigma Chemical, St. Louis, MO) or trypsin. MMP-9 also was activated using human

recombinant MMP-3 (purified in Assignee's laboratory following standard cloning and purification techniques).

[1058] Two fluorogenic, methoxycoumarin-containing polypeptide substrates were used in the MMP inhibition assays:

$$\text{MCA-ProLeuGlyLeuDpaAlaArgNH}_2$$

(I)

$$\text{MCA-ArgProLeuGlyLeuDpaAlaArgGluArgNH}_2$$

(II)

Here, "Dpa" is 3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl group, and "MCA" is 7-methoxycoumarin-4-yl acetyl. Substrate (I) was purchased from Baychem (Redwood City, CA), and substrate II was prepared Assignee's laboratory. Substrate I was used in the IC_{50} determination assays, while substrate II was used in the K_i determination assays. In the absence of MMP inhibitory activity, either substrate is cleaved at the Gly-Leu peptide bond. This cleavage separates the highly fluorogenic peptide from the 2,4-dinitrophenyl quencher, thus resulting in increase of fluorescent intensity.

[1059] The stock solutions of the assayed hydroxamates (or salts thereof) were prepared in 1% dimethyl sulfoxide (DMSO). These stock solutions were diluted in Buffer A (100 mM Tris-HCl, 100 mM NaCl, 10 mM $CaCl_2$, 0.05% polyoxyethylene 23 lauryl ether, pH 7.5) to obtain solutions with different hydroxamate concentrations, *i.e.*, assay solutions with different concentrations of the assayed MMP inhibitory compound. The experiment controls contained the same amount of Buffer A/DMSO as the assayed sample, but contained no hydroxamate (or salt thereof).

[1060] The assays from which the IC_{50} determinations were made were performed as follows. The MMPs were activated with either trypsin or APMA (4-aminophenylmercuric acetate, Sigma Chemical, St. Louis, MO). The assayed hydroxamate samples were incubated in Microfluor™ White Plates (Dynatech, Chantilly, VA) and analyzed on a Perkin Elmer L550 plate reader (Norwalk, CT). The excitation wavelength was 328 nm, and the emission wavelength – 415 nm. All samples (assayed hydroxamates and controls) were incubated in separate plates at room temperature in the presence of 4 μM of MMP substrate (I). As stated in the previous paragraph, samples containing varying concentrations of the same assayed hydroxamate were prepared.

Inhibition was measured as a reduction in fluorescent intensity as a function of MMP inhibitor concentration.

[1061] The assays from which the K_i determinations were made were performed as follows. The assayed hydroxamate samples were incubated in separate wells of untreated white polystyrene plates (Nunc Nalgene International, Rochester, NY), and analyzed on a Tecan SpectraFlour Plus plate reader. The excitation wavelength was 330 nm, and the emission wavelength – 420 nm. All samples (assayed hydroxamates and controls) were incubated in separate plate wells at room temperature for 1 hr in the presence of 4 μM of MMP substrate (II). In the absence of MMP inhibitory activity, substrate II was cleaved at the Gly-Leu bond resulting in an increase of relative fluorescence. Inhibition was observed as a reduced rate of this increase in relative fluorescence. The various hydroxamates were analyzed using a single low enzyme concentration with a single substrate concentration fixed at or below the K_m. This protocol is a modification of method by Knight et al., *FEBS Lett.*, 296(3), 263-266 (1992). Apparent inhibitory constants were determined by non-linear regression of reaction velocity as a function of inhibitor and enzyme concentration using Morrison's equation, as described by Kuzmic, Anal. Biochem. 286, 45-50 (2000). Modifications were made in the non-linear regression method to allow a common control reaction rate and effective enzyme concentration to be shared between all dose-response relationships on a given assay plate. Since the substrate concentration was chosen to be at or below the K_m, the apparent K_i's from this analysis were reported as K_i's without correction for the influence of substrate.

[1062] The above protocols were used to determine IC50 constants and K_i values values for several of the compounds in **Examples 1-52** above. The results are shown in Table 5. All values in **Table 5** are given in nM units. The K_i measurements are in parenthesis.

Table 5

Ex. #	Compound	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
55	Example 17		550		1.6	
56	Example 18	>10000	537	6000	1.8	>10000
57	Example 19	>10000	9000	5190	15	>10000
58	Example 20	>10000	1.8	498	1.8	>10000
59	Example 21	>10000	450	>10000	3.5	>10000
60	Example 22	>10000	1000	>10000	4.9	>10000

Ex. #	Compound	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
61	Example 25	>10000	247.2	8498	1.8	>10000
62	Example 26	>10000	52.0	4429	3.4	>10000
63	Example 27	>10000	83.9	9366	0.2	>10000
64	Example 28	>10000	76.4	3710	7.0	>10000
65	Example 30	>10000	22.6	809	1.3	>10000
66	Example 31	>10000 (>10000)	346.3 (412.93)	5651 (1596.8)	2.1 (1.503)	>10000 (>10000)
67	Example 32	>10000	217.7	4076	0.8	>10000
68	Example 33	>10000	16	7.9	1	4936
69	Example 34	429	36.6	>10000	3.0	>10000
70	Example 35	>10000	600	>10000	3	>10000
71	Example 36		95		2.4	
72	Example 37	8708	30.3	449	1.4	>10000
73	Example 38	>10000 (>10000)	157.5	1026.3 (369.98)	0.9 (6.55)	>10000 (4451.2)
74	Example 39	(>10000)	1299 (1640)	(2360)	0.9 (3.04)	(>10000)
75	Example 40	>10000 (>10000)	112.4 (215.98)	413 (585.44)	0.5 0.58)	>10000 (>10000)
76	Example 41	>10000 (>10000)	357.5 (414.99)	1597 (1465.7)	2.0 (1.056)	>10000 (>10000)
77	Example 42	>10000 (>10000)	100.3 (186.28)	382.5 (661.7)	0.3 (0.486)	>10000 (>10000)
78	Example 43	>10000	4.8	1.0	1.0	2084
79	Example 44	>10000	133.2	154.5	1.4	4976
80	Example 45	(>10000)	(224.78)	(499.18)	(0.62)	(>10000)
81	Example 46	>10000 (>10000)	320.9 (786.36)	1966 (417.51)	3.1 (2.29)	>10000 (>10000)
82	Example 47	(>10000)	18.2 (19.15) (46.49)	(118.75) (308.77)	0.2 (0.304) (0.423)	(3317.66) (5293)
83	Example 48	>10000 (>10000)	104.6 (227.54)	4450.3 (159.2)	0.2 (0.127)	>10000 (>10000)
84	Example 49	>10000 (>10000)	273.9 (439.76)	4056 (1947.90)	0.3 (0.439)	>10000 (>10000)
85	Example 50	(>10000)	(1127.89)	(304.41)	(0.60)	(>10000)
86	Example 51	>10000 (5160.20)	251.6 (93.68)	7983 (98.72)	0.2 (1.697)	>10000 (687.93)
87	Example 52	(>10000)	(542.89)	(617.14)	(0.81)	(>10000)
88	Example 53	>10000 (>10000)	383.5 (697)	75.5 (2900)	1.0 (0.662)	>10000 (>10000)
89	Example 54	(>10000)	35.5 (64.8)	(388)	10.5	(4120)

[1063] **Example 90. *In Vivo* Angiogenesis Assay**

[1064] The study of angiogenesis depends on a reliable and reproducible model for the stimulation and inhibition of a neovascular response. The corneal micropocket assay provides such a model of angiogenesis in the cornea of a mouse. *See, A Model of Angiogenesis in the Mouse Cornea*; Kenyon,BM, et al., Investigative Ophthalmology & Visual Science, July 1996, Vol. 37, No. 8.

[1065] In this assay, uniformLy sized Hydron™ pellets containing bFGF and sucralfate are prepared and surgically implanted into the stroma mouse cornea adjacent to the temporal limbus. The pellets are formed by making a suspension of 20 μL sterile saline containing 10 μg recombinant bFGF, 10 mg of sucralfate and 10 μL of 12 percent Hydron™ in ethanol. The slurry is then deposited on a 10 x 10 mm piece of sterile nylon mesh. After drying, the nylon fibers of the mesh are separated to release the pellets.

[1066] The corneal pocket is made by anesthetizing a 7 week old C57Bl/6 female mouse, then proptosing the eye with a jeweler's forceps. Using a dissecting microscope, a central, intrastromal linear keratotomy of approximately 0.6 mm in length is performed with a #15 surgical blade, parallel to the insertion of the lateral rectus muscle. Using a modified cataract knife, a lamellar micropocket is dissected toward the temporal limbus. The pocket is extended to within 1.0 mm of the temporal limbus. A single pellet is placed on the corneal surface at the base of the pocket with a jeweler's forceps. The pellet is then advanced to the temporal end of the pocket. Antibiotic ointment is then applied to the eye.

[1067] Mice are dosed on a daily basis for the duration of the assay. Dosing of the animals is based on bioavailability and overall potency of the compound. An exemplary dose is 10 or 50 mg/kg (mpk) bid, po. Neovascularization of the corneal stroma is permitted to continue under the influence of the assayed compound for 2 days. At that point, the degree of angiogenic inhibition is scored by viewing the neovascular progression with a slit lamp microscope.

[1068] The mice are anesthetized and the studied eye is once again proptosed. The maximum vessel length of neovascularization, extending from the limbal vascular plexus toward the pellet is measured. In addition, the contiguous circumferential zone of neovascularization is measured as clock hours, where 30 degrees of arc equals one clock hour. The area of angiogenesis is calculated as follows.

$$\text{area} = \frac{(0.4\text{xclock hours x } 3.14 \text{ x vessel length (in mm)})}{2}$$

[1069] Five to six mice should be utilized for each compound in each study. The studied mice are thereafter compared to control mice and the difference in the area of neovascularization is recorded as an averaged value. Each group of mice so studied constitutes an "n" value of one, so that "n" values greater than one represent multiple studies whose averaged result is provided in the table. A contemplated compound typically exhibits about 25 to about 75 percent inhibition, whereas the vehicle control exhibits zero percent inhibition.

[1070] **Example 91. Tumor Necrosis Factor Assays**

[1071] Cell Culture.

[1072] The cells used in the assay are the human moncytic line U-937 (ATCC CRL-1593). The cells are grown in RPMI w/10% FCS and PSG supplement (R-10) and are not permitted to overgrow. The assay is carried out as follows:

[1073] 1. Count, then harvest cells by centrifugation. Resuspend the pellet in R-10 supplement to a concentration of 1.540 x 10^6 cells/mL.

[1074] 2. Add test compound in 65 uL R-10 to the appropriate wells of a 96-well flat bottom tissue culture plate. The initial dilution from a DMSO stock (100 mM compound) provides a 400 uM solution, from which five additional three-fold serial dilutions are made. Each dilution of 65 ul (in triplicate) yields final compound test concentrations of 100 μM, 33.3 μM, 11.1 μM, 3.7 μM, 1.2 μM and 0.4 μM.

[1075] 3. The counted, washed and resuspended cells (200,000 cells/well) in 130 μL are added to the wells.

[1076] 4. Incubation is for 45 min to 1 hr at 37°C in 5% CO_2 in a water saturated container.

[1077] 5. R-10 (65 uL)containing 160 ng/mL PMA (Sigma) is added to each well.

[1078] 6. The test system is incubated at 37°C in 5% CO2 overnight (18-20 hr) under 100% humidity.

[1079] 7. Supernatant, 150 μL, is carefully removed from each well for use in the ELISA assay.

[1080] 8. For toxicity, a 50 μL aliquot of working solution containg 5 mL R-10, 5 mL MTS solution [CellTiter 96 AQueous One Solution Cell Proliferation Assay Cat.#G358/0,1 (Promega Biotech)] and 250 ul PMS solution are added to each well containing the remaining supernatant and cells and the cells incubated at 37°C in 5% CO_2 until the color develops. The system is excited at 570 nm and read at 630 nm.

[1081] TNF Receptor II ELISA Assay

[1082] 1. Plate 100 μL/well 2 ug/mL mouse anti-human TNFrII antibody (R&D Systems #MAB226) in 1 x PBS (pH 7.1, Gibco) on NUNC-Immuno Maxisorb plate. Incubate the plate at 4°C overnight (about 18-20 hr).

[1083] 2. Wash the plate with PBS-Tween (1 x PBS w/ 0.05% Tween).

[1084] 3. Add 200 μL 5% BSA in PBS and block at 37°C in a water saturated atmosphere for 2 hr.

[1085] 4. Wash the plate with PBS-Tween.

[1086] 5. Add sample and controls (100 ul of each) to each well. The standards are 0, 50, 100, 200, 300 and 500 pg recombinant human TNFrII (R&D Systems #226-B2) in 100 μL 0.5% BSA in PBS. The assay is linear to between 400-500 pg of standard.

[1087] 6. Incubate at 37°C in a saturated atmosphere for 1.5 hr.

[1088] 7. Wash the plate with PBS-Tween.

[1089] 8. Add 100 μL goat anti-human TNFrII polyclonal (1.5 μg/mL R&D Systems #AB226-PB in 0.5% BSA in PBS).

[1090] 9. Incubate at 37°C in a saturated atmosphere for 1 hr.

[1091] 10. Wash the plate with PBS-Tween.

[1092] 11. Add 100 μL anti-goat IgG-peroxidase (1:50,000 in 0.5% BSA in PBS, Sigma #A5420).

[1093] 12. Incubate at 37°C in a saturated atmosphere for 1 hr.

[1094] 13. Wash the plate with PBS-Tween.

[1095] 14. Add 10 μL KPL TMB developer, develop at room temperature (usually about 10 min), then terminate with phosphoric acid and excite at 450 nm and read at 570 nm.

[1096] TNFα ELISA Assay.

[1097] Coat Immulon® 2 plates with 0.1 mL/well of 1ug/mL Genzyme mAb in 0.1 M NaHCO3 pH 8.0 buffer overnight (about 18-20 hr) at 4°C, wrapped tightly in Saran® wrap.

[1098] Flick out coating solution and block plates with 0.3 mL/well blocking buffer overnight at 4°C, wrapped in Saran® wrap.

[1099] Wash wells thoroughly 4X with wash buffer and completely remove all wash buffer. Add 0.1 mL/well of either samples or rhTNFα standards. Dilute samples if necessary in appropriate diluant (e.g. tissue culture medium). Dilute standard in same diluant. Standards and samples should be in triplicates.

[1100] Incubate at 37°C for 1 hr in humified container.

[1101] Wash plates as above. Add 0.1 mL/well of 1:200 dilution of Genzyme rabbit anti-hTNFa.

[1102] Repeat incubation.

[1103] Repeat wash. Add 0.1 mL/well of 1 μg/mL Jackson goat anti-rabbit IgG (H+L)-peroxidase.

[1104] Incubate at 37°C for 30 min.

[1105] Repeat wash. Add 0.1 mL/well of peroxide-ABTS solution.

[1106] Incubate at room temperature for 5-20 min.

[1107] Read OD at 405 nm.

[1108] 12 Reagents are:

Genzyme mouse anti-human TNF monoclonal (Cat.# 80-3399-01)

Genzyme rabbit anti-human TNF polyclonal (Cat.#IP-300)

Genzyme recombinant human TNF (Cat.#TNF-H).

Jackson Immunoresearch peroxide-conjugated goat anti-rabbit IgG (H+L) (Cat.#111-035-144).

Kirkegaard/Perry peroxide ABTS solution (Cat#50-66-01).

Immulon 2 96-well microtiter plates.

Blocking solution is 1 mg/mL gelatin in PBS with 1X thimerasol.

Wash buffer is 0.5 mL Tween® 20 in 1 liter ofPBS.

[1109] Example 92. *In Vitro* Aggrecanase Inhibition Analysis

[1110] Assays for measuring the potency (IC_{50}) of a compound toward inhibiting aggrecanase are known in the art.

[1111] One such assay, for example, is reported in European Patent Application Publ. No. EP 1 081 137 A1. In that assay, primary porcine chondrocytes from articular joint cartilage are isolated by sequential trypsin and collagenase digestion followed by collagenase digestion overnight and are plated at $2x10^5$ cells per well into 48 well plates with 5 μCi/ml ^{35}S (1000 Ci/mmol) sulphur in type 1 collagen coated plates. Cells are allowed to incorporate label into their proteoglycan matrix (approximately 1 week) at 37°C under an atmosphere of 5% CO_2. The night before initiating the assay, chondrocyte monolayers are washed 2 times in DMEM/1% PSF/G and then allowed to incubate in fresh DMEM/1% FBS overnight. The next morning, chondrocytes are washed once in DMEM/1% PSF/G. The final wash is allowed to sit on the plates in the incubator while making dilutions. Media and dilutions are made as described in the following Table 6:

Table 6

control media	DMEM alone
IL-1 media	DMEM + IL-1 (5ng/ml)

drug dilutions	Make all compound stocks at 10 mM in DMSO. Make a 100 μM stock of each compound in DMEM in 96-well plate. Store in freezer overnight. The next day, perform serial dilutions in DMEM with IL-1 to 5 μM, 500 nM, and 50 nM. Aspirate final wash from wells and add 50 μM of compound from above dilutions to 450 μL of IL-1 media in appropriate wells of the 48 well plates. Final compound concentrations equal 500 nM, 50 nM, and 5 nM. All samples completed in triplicate with control and IL-1 alone on each plate.

Plates are labeled and only the interior 24 wells of the plate are used. On one of the plates, several columns are designated as IL-1 (no drug) and control (no IL-1, no drug). These control columns are periodically counted to monitor 35S-proteoglycan release. Control and IL-1 media are added to wells (450 μL) followed by compound (50 μL) so as to initiate the assay. Plates are incubated at 37°C with 5% CO_2 atmosphere. At 40-50% release (when CPM from IL-1 media is 4-5 times control media) as assessed by liquid scintillation counting (LSC) of media samples, the assay is terminated (about 9 to about 12 hours). Media is removed from all wells and placed into scintillation tubes. Scintillate is added and radioactive counts are acquired (LSC). To solubilize cell layers, 500 μL of papain digestion buffer (0.2 M Tris, pH 7.0, 5 mM DTT, and 1 mg/ml papain) is added to each well. Plates with digestion solution are incubated at 60°C overnight. The cell layer is removed from the plates the next day and placed in scintillation tubes. Scintillate is then added, and samples counted (LSC). The percent of released counts from the total present in each well is determined. Averages of the triplicates are made with control background subtracted from each well. The percent of compound inhibition is based on IL-1 samples as 0% inhibition (100% of total counts).

[1112] Another assay for measuring aggrecanase inhibition is reported in WIPO Int'l Publ. No. WO 00/59874. That assay reportedly uses active aggrecanase accumulated in media from stimulated bovine cartilage (BNC) or related cartilage sources and purified

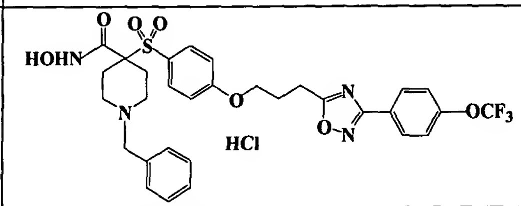
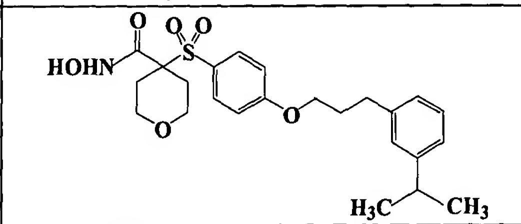
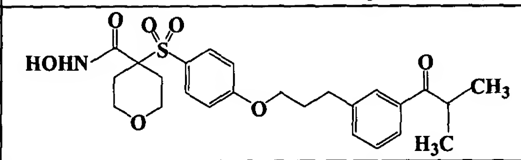
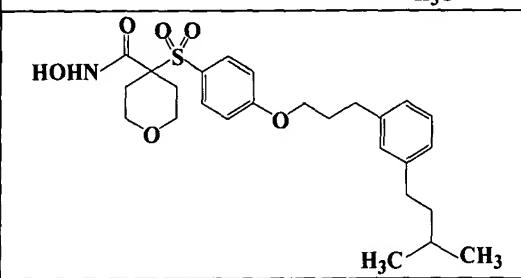
cartilage aggrecan monomer or a fragment thereof as a substrate. Aggrecanase is generated by stimulation of cartilage slices with interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), or other stimuli. To accumulate BNC aggrecanase in culture media, cartilage reportedly is first depleted of endogenous aggrecan by stimulation with 500 ng/ml human recombinant IL-β for 6 days with media changes every 2 days. Cartilage is then stimulated for an additional 8 days without media change to allow accumulation of soluble, active aggrecanase in the culture media. To decrease the amounts of matrix metalloproteinases released into the media during aggrecanase accumulation, agents which inhibit MMP-1, -2, -3, and -9 biosynthesis are included during stimulation. This BNC conditioned media containing aggrecanase activity is then used as the source of aggrecanase for the assay. Aggrecanase enzymatic activity is detected by monitoring production of aggrecan fragments produced exclusively by cleavage at the Glu373-Ala374 bond within the aggrecan core protein by Western analysis using the monoclonal antibody, BC-3 (Hughes, et al., *Biochem J*, 306:799-804 (1995)). This antibody reportedly recognizes aggrecan fragments with the N-terminus, 374ARGSVIL, generated upon cleavage by aggrecanase. The BC-3 antibody reportedly recognizes this neoepitope only when it is at the N-terminus and not when it is present internally within aggrecan fragments or within the aggrecan protein core. Only products produced upon cleavage by aggrecanase reportedly are detected. Kinetic studies using this assay reportedly yield a Km of 1.5+/-0.35 μM for aggrecanase. To evaluate inhibition of aggrecanase, compounds are prepared as 10 mM stocks in DMSO, water, or other solvents and diluted to appropriate concentrations in water. Drug (50 μL) is added to 50 μL of aggrecanase-containing media and 50 μL of 2 mg/ml aggrecan substrate and brought to a final volume of 200 μL in 0.2 M Tris, pH 7.6, containing 0.4 M NaCl and 40 mM $CaCl_2$. The assay is run for 4 hr at 37°C, quenched with 20 mM EDTA, and analyzed for aggrecanase-generated products. A sample containing enzyme and substrate without drug is included as a positive control and enzyme incubated in the absence of substrate serves as a measure of background. Removal of the glycosaminoglycan side chains from aggrecan reportedly is necessary for the BC-3 antibody to recognize the ARGSVIL epitope on the core protein. Therefore, for analysis of aggrecan fragments generated by cleavage at the Glu373-Ala374 site, proteoglycans and proteoglycan fragments are enzymatically deglycosylated with chondroitinase ABC (0.1 units/10 μg GAG) for 2 hr at 37°C and then with keratanase (0.1

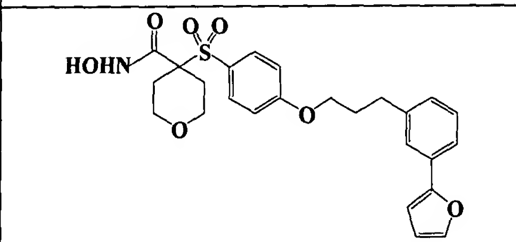
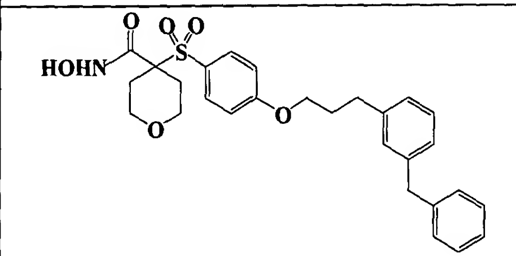
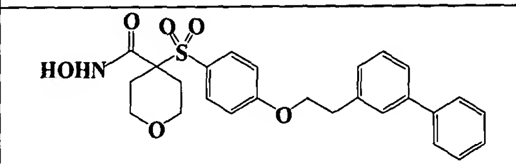
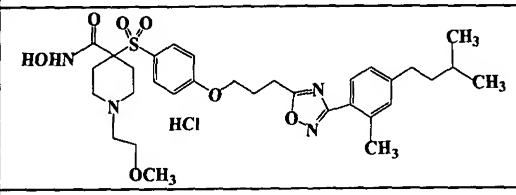
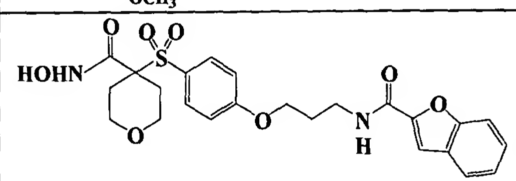
units/10 μg GAG) and keratanase II (0.002 units/10 μg GAG) for 2 hr at 37°C in buffer containing 50 mM sodium acetate, 0.1 M Tris/HCl, pH 6.5. After digestion, aggrecan in the samples is precipitated with 5 volumes of acetone and resuspended in 30 μL of Tris glycine SDS sample buffer (Novex) containing 2.5% beta mercaptoethanol. Samples are loaded and then separated by SDS-PAGE under reducing conditions with 4-12% gradient gels, transferred to nitrocellulose and immunolocated with 1:500 dilution of antibody BC3. Subsequently, membranes are incubated with a 1:5000 dilution of goat anti-mouse IgG alkaline phosphatase second antibody and aggrecan catabolites visualized by incubation with appropriate substrate for 10-30 minutes to achieve optimal color development. Blots are quantitated by scanning densitometry and inhibition of aggrecanase determined by comparing the amount of product produced in the presence versus absence of compound.

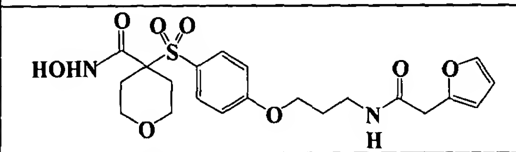
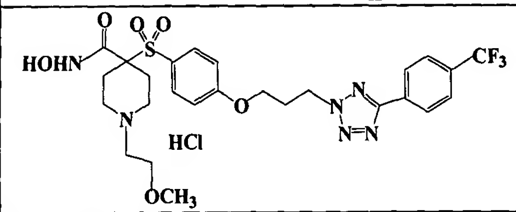
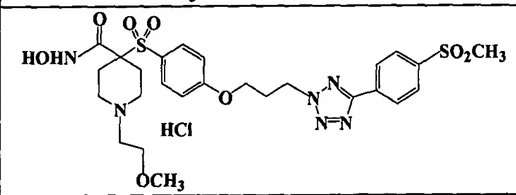
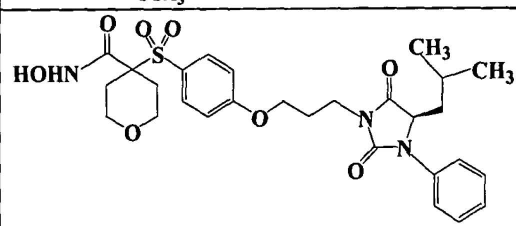
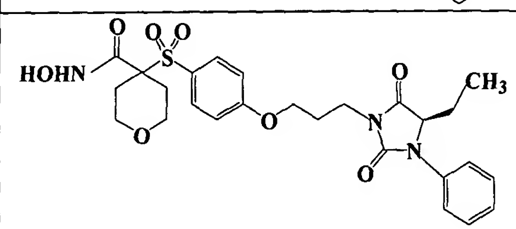
[1113] **Examples 93-645.**

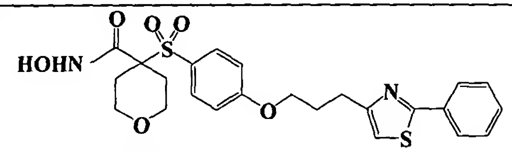
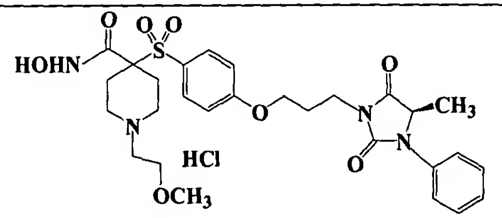
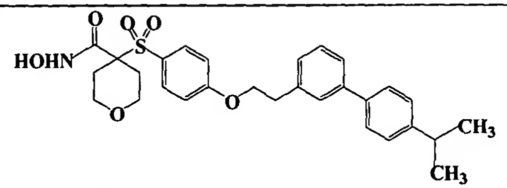
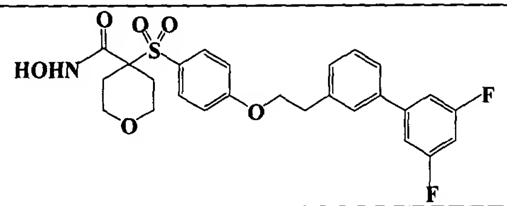
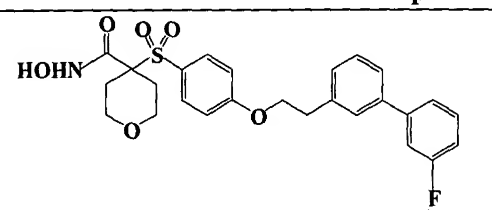
[1114] Additional hydroxamate compounds (and salts thereof) can be prepared by one skilled in the art using methods similar to those described in **Examples 1-54** alone or in combination with techniques well known in the art. Such compounds include, for example, the compounds summarized in the following **Table 7**. **Table 7** also summarizes *in vitro* MMP inhibition results obtained by Applicants with the listed hydroxamates. As with **Table 5**, all *in vitro* K_i and IC_{50} results in **Table 7** are given in nM units. The Ki measurements are in parenthesis.

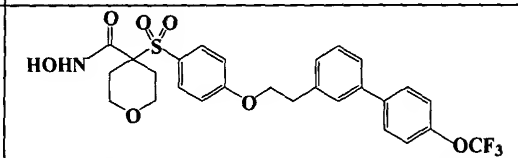
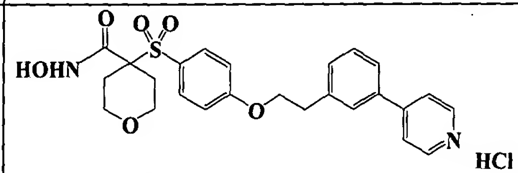
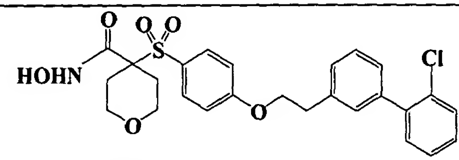
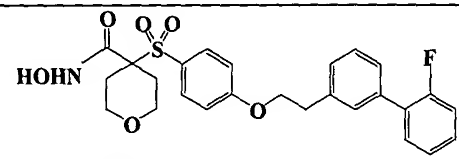
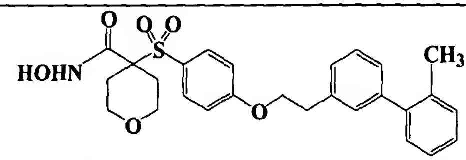
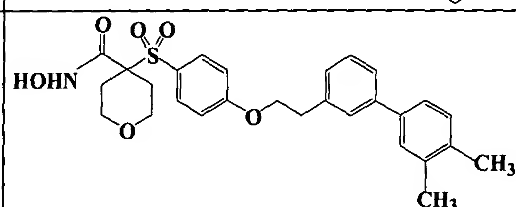
Table 7

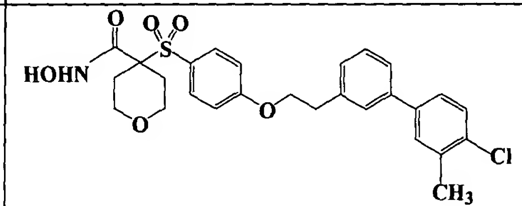
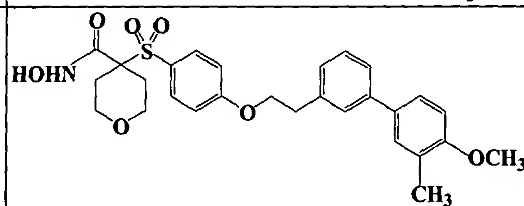
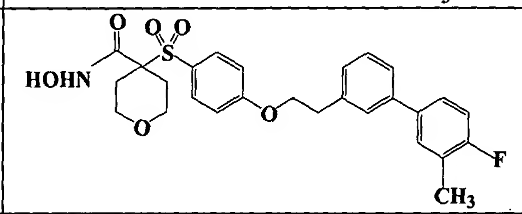
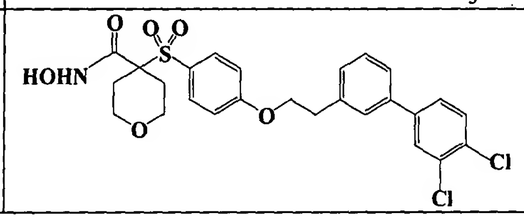
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
93				(>10000)	746.6 (676)	(1120)	15.5 (9.29)	(>10000)
94					17.8		3.7	
95				>10000 (>10000)	91.4 (149)	1204.6 (788)	2.7	>10000 (5410)
96					39.1		15.3	

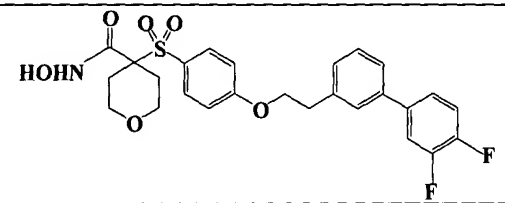
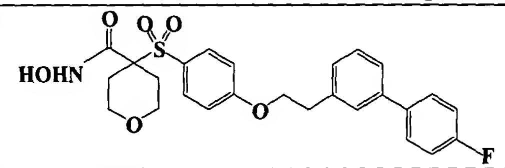
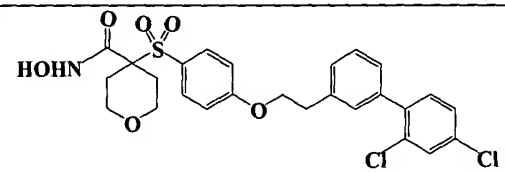
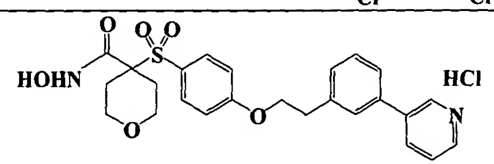
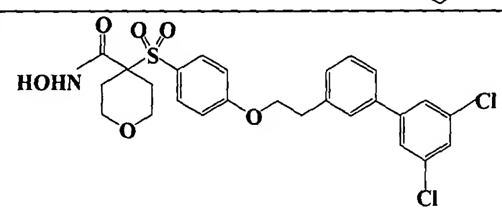
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
97		486.1586	486.1602	(7360)	185.0 (295)	(473)	3.3 (5.57)	(>10000)
98		510.1950	510.1947	>10000 (>10000)	316.2 (625)	2418 (1450)	1.8 (9.15)	>10000 (>10000)
99		482.1637	482.1661	>10000	245.8	3435	0.4	>10000
100					1691.4		152.6	
101		503.1480	503.1465		18.2		0.2	

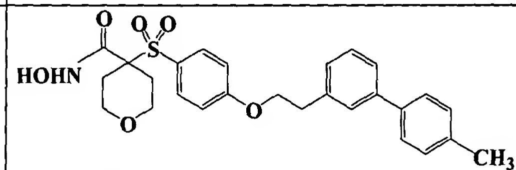
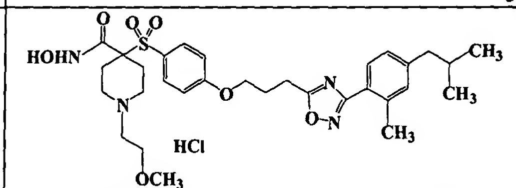
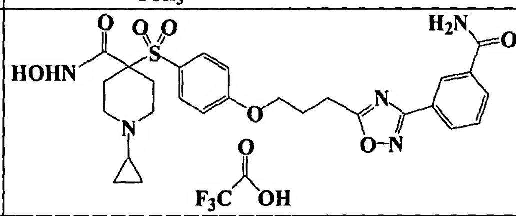
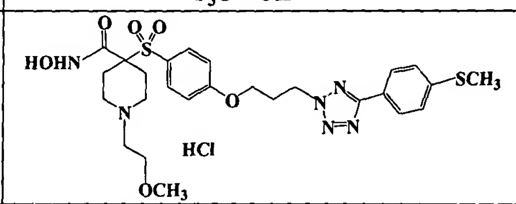
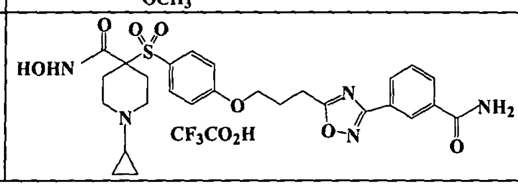
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
102		483.1260	483.1264		12.4		1.2	
103		613	613	>10000	85.8	1134	0.4	>10000
104					44.2		0.8	
105				>10000	1368.8	7694	9.7	>10000
106				>10000	1046.6	>10000	3.5	>10000

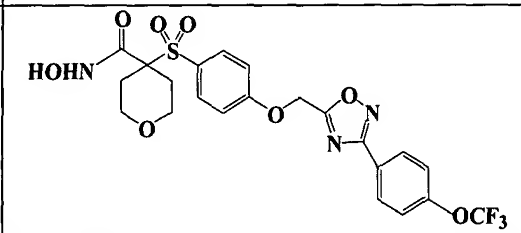
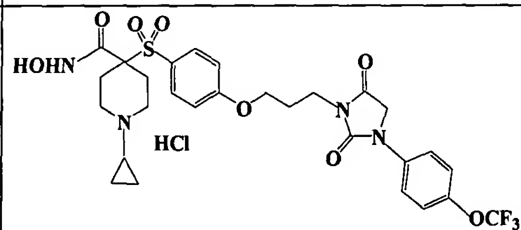
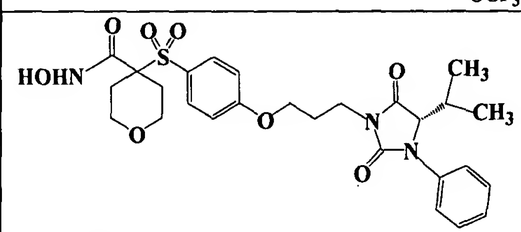
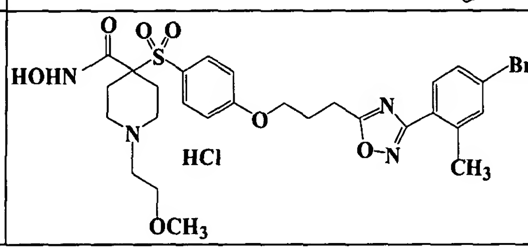
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
107					34.0		5.5	
108					433.7		20.0	
109		524.2107	524.2136	(>10000)	5410.3 (8100)	(>10000)	152.1 (93.1)	(>10000)
110		518.1449	518.1505	(>10000)	1198.5 (1120)	(4340)	7.6 (11.4)	(>10000)
111		500.1543	500.1561	(>10000)	559.4 (769)	(2680)	2.0 (6.39)	(>10000)

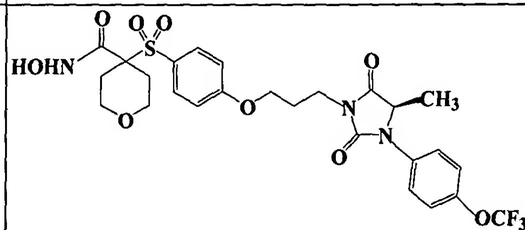
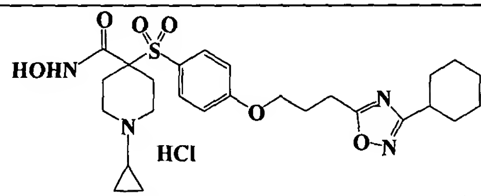
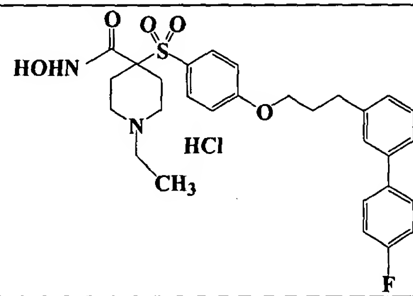
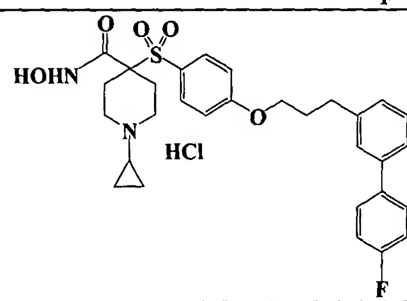
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
112		566.1460	566.1500	(>10000)	66.4 (3970)	(8850)	37.9 (51.2)	(>10000)
113		483.1590	483.1597	>10000 (>10000)	20.3 (42.30)	1980.5 (161.22)	0.2 (0.312)	7725 (3481.8)
114		516.1248	516.1259	(>10000)	1010.6 (1500)	(4870)	5.2 (4.2)	(>10000)
115		500.1543	500.1550	>10000 (>10000)	311.9 (807)	>10000 (1980)	0.9 (2.24)	>10000 (>10000)
116		496.1794	496.1811	(>10000)	1053.2 (1250)	(5550)	11.2 (5.1)	(>10000)
117		510.1950	510.1965	(>10000)	1744.7 (3640)	(9910)	16.0 (21)	(>10000)

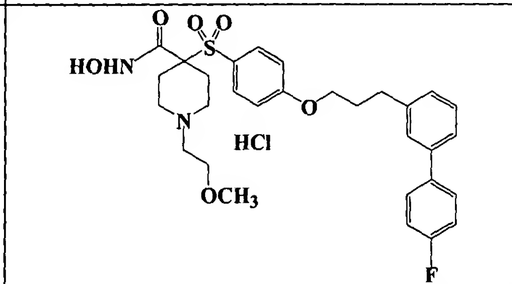
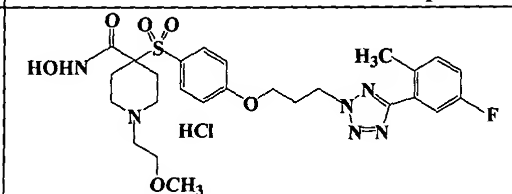
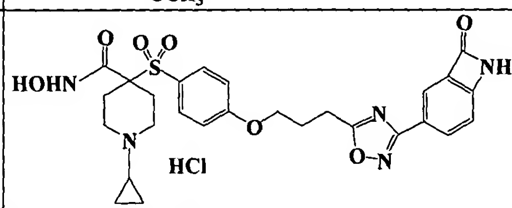
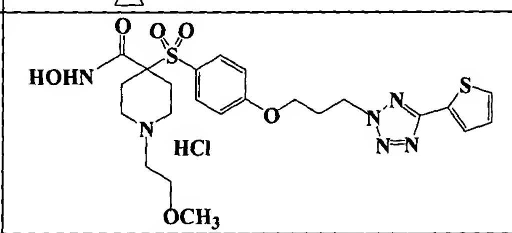
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
118		530.1404	530.1418	(>10000)	1862.0 (2650)	(>10000)	29.8 (18.8)	(>10000)
119		526.1899	526.1920	(>10000)	1187.6 (1680)	(3950)	18.3 (31.4)	(>10000)
120		514.1700	514.1724	>10000	1171.6	>10000	5.8	>10000
121		550.0858	550.0846	(>10000)	2469.3 (4620)	(>10000)	21.6 (26.9)	(>10000)

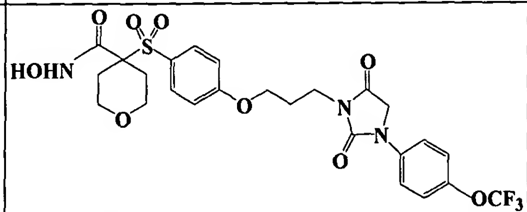
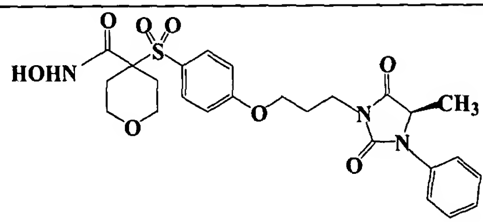
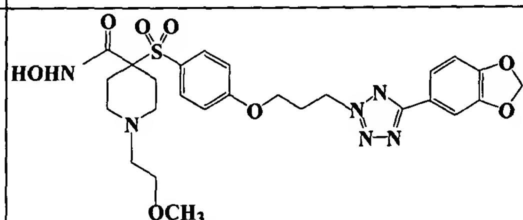
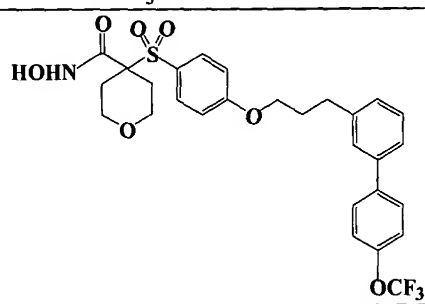
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
122		518.1449	518.1470	>10000	759.7	7668	1.9	>10000
123		500.1543	500.1545	>10000 (>10000)	383.0 (793)	>10000 (2130)	1.4 (7.35)	>10000 (>10000)
124		550.0858	550.0896	(>10000)	2151.5 (5730)	(>10000)	21.9 (20.1)	(>10000)
125				2937 (3584.24)	27.3 (51.34)	962.9 (146.43)	0.2 (0.17)	5825 (1666.65)
126		550.0858	550.0881	(>10000)	3260.4 (6360)	(>10000)	349.0 (81.3)	(>10000)

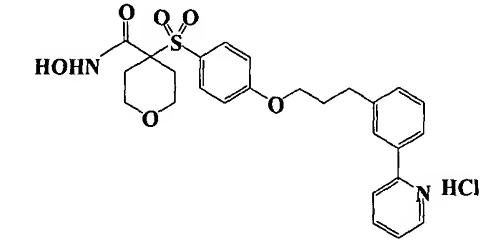
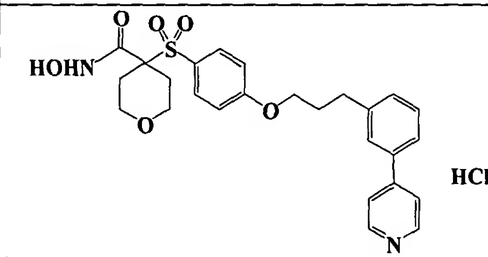
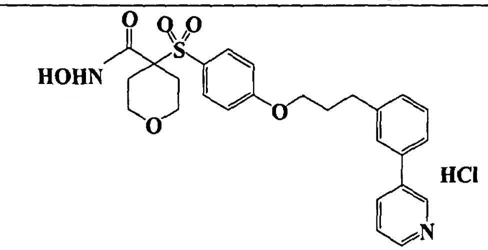
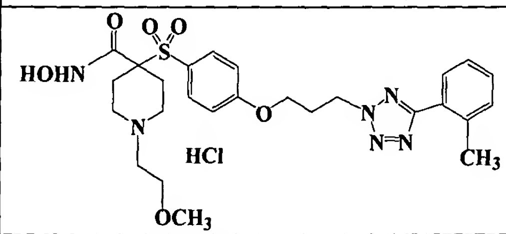
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
127		496.1794	496.1800	>10000 (>10000)	1380.0 (2160)	>10000 (4230)	5.5 (16.2)	>10000 (>10000)
128		615.2902	615.2852	(>10000)	658.7 (1130)	(3550)	23.7 (13.8)	(>10000)
129				(>10000)	41.4 (50)	(110)	1.9 (0.27)	(>10000)
130				4611	4.7	50.2	0.3	499.8
131					107.9		4.5	

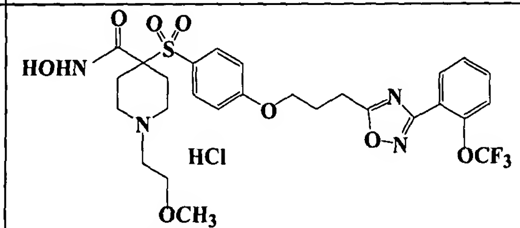
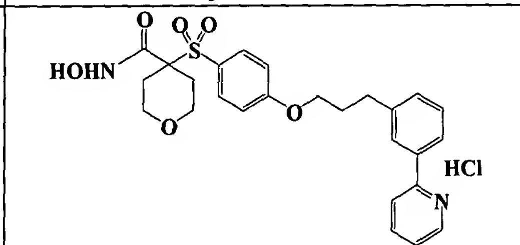
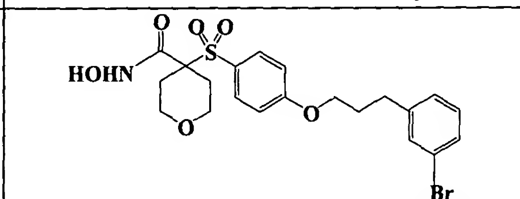
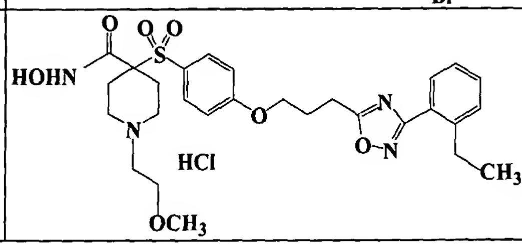
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
132					61.7		3.7	
133					84.4		4.3	
134				>10000	2382	>10000	7.7	>10000
135		637.1332	637.1315	(>10000)	24.3 (58.5)	(457)	2.9 (0.761)	(9510)

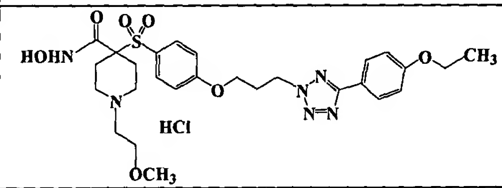
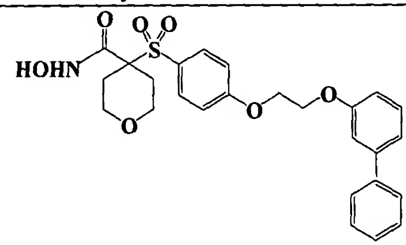
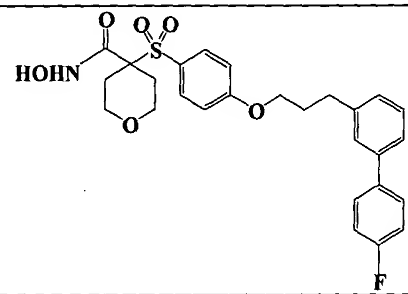
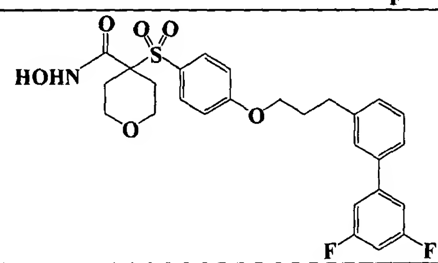
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
136					229.4		4.4	
137				(>10000)	20.4 (36.6)	(604)	7.0 (0.976)	(>10000)
138				>10000	247.3	1896	2.1	>10000
139		553.2172	553.2176	>10000 (>10000)	207.7 (1410)	4514 (1390)	0.4 (2.89)	>10000 (>10000)

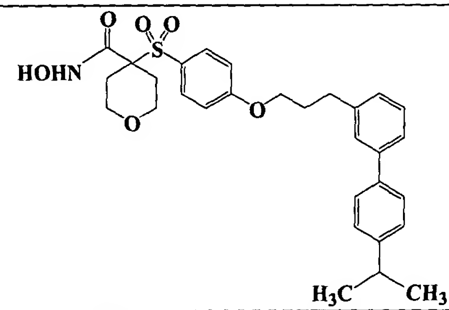
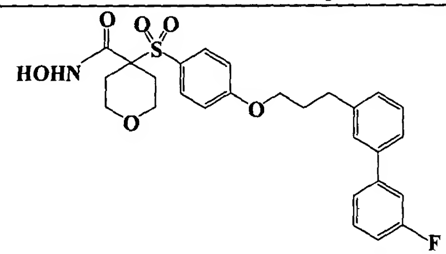
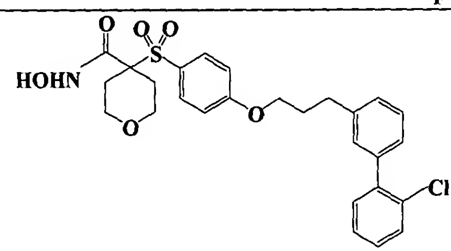
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
140				>10000 (>10000)	48.0 (708)	1692 (754)	0.5 (0.895)	>10000 (>10000)
141		577	577		32.5		3.6	
142				(>10000)	58.6 (96.4)	(310)	7.5 (1.34)	(>10000)
143					4.9		1.4	

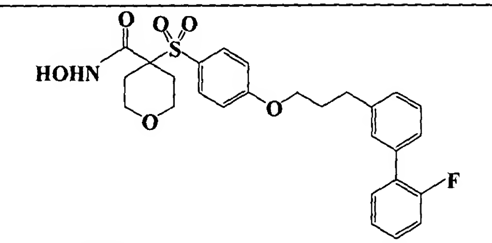
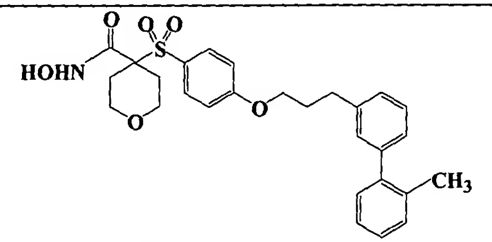
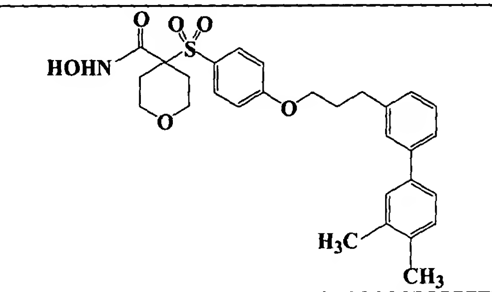
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
144				>10000	238.6	5989	2.5	>10000
145				>10000	816.9	9438	2.0	>10000
146					11.1		0.4	
147		580.1617	580.1620	(>10000)	4746.8 (>10000)	(7970)	28.3 (23.9)	(>10000)

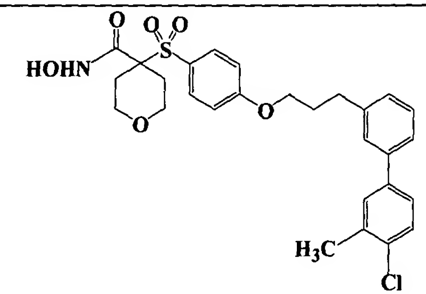
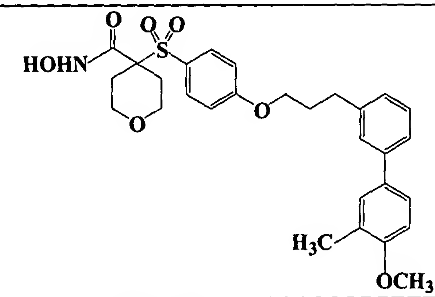
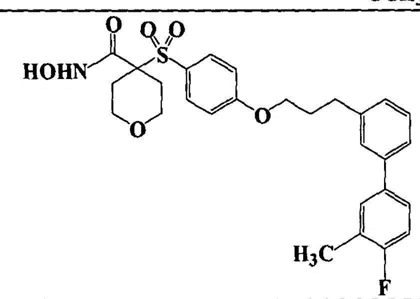
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
148				(8790)	272.0 (213)	(427)	3.1 (1.72)	(5150)
149				(>10000)	77.1 (84.1)	(94.5)	1.3 (1.18)	(2530)
150				>10000 (>10000)	135.5 (159)	529.9 (125)	0.6 (0.587)	6630 (5510)
151		559	559		38.4		2.6	

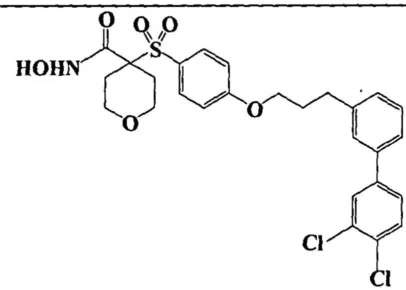
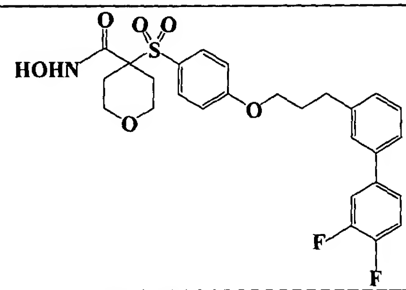
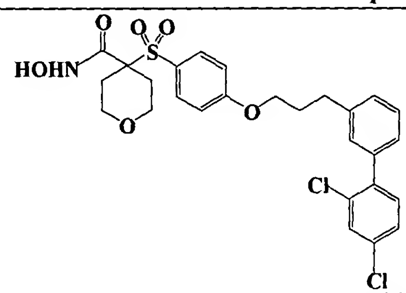
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
152		629.1893	629.1885	>10000 (>10000)	58.8 (149)	72.3 (44.5)	11.8 (2.66)	>10000 (>10000)
153					192.5		7.6	
154		498.0586	498.0591	>10000 (>10000)	10.9 (33.9)	111 (151)	0.8 (0.95)	9123 (3910)
155		573.2383	573.2413	>10000 (>10000)	13.8 (37.9)	1173.7 (172)	9.7 (1.58)	>10000 (9370)

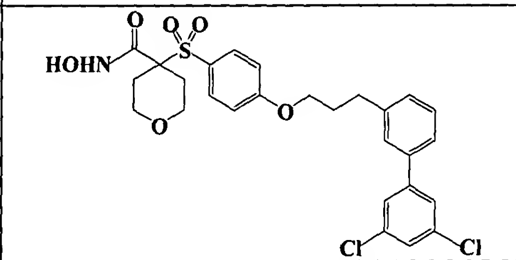
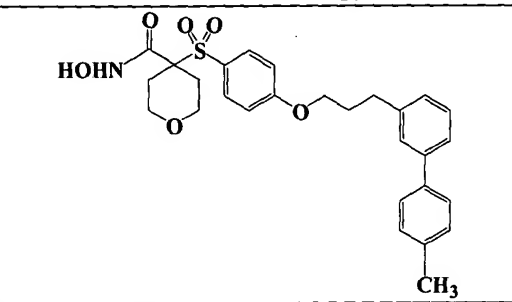
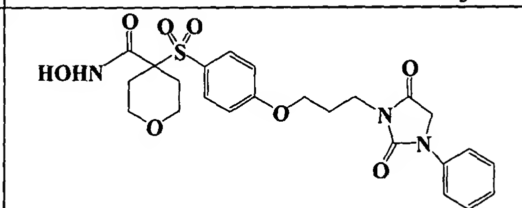
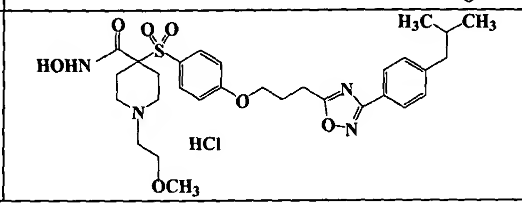
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
156					32.1		1.0	
157				>10000 (>10000)	182.1 (419)	2473 (1390)	3.5 (4.01)	>10000 (>10000)
158		530.1404	530.1446	>10000 (>10000)	2184 (2730)	5630 (3950)	3.6 (5.1)	>10000 (>10000)
159		532.1605	532.1632		1368.6		24.4	

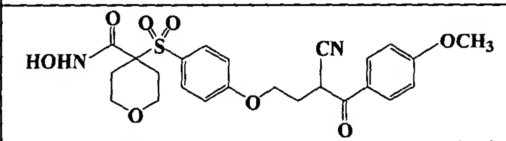
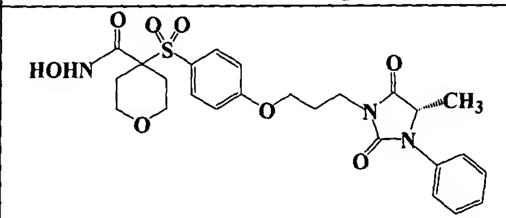
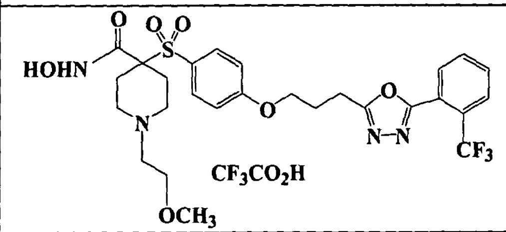
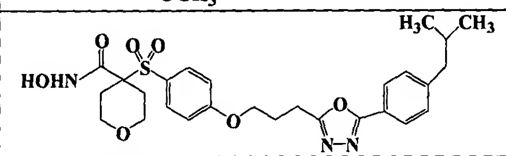
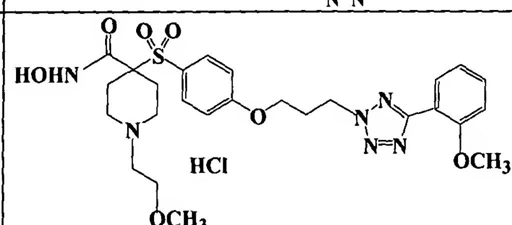
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
160		538.2263	538.2275	>10000 (>10000)	>10000 (>10000)	(>10000)	505.1	(>10000)
161		514.1700	514.1708	>10000 (>10000)	1001.1 (1760)	2625 (1730)	2.6 (20.3)	>10000
162		530.1404	530.1428	(>10000)	1596.6 (2370)	(3150)	15.6 (12)	(>10000)

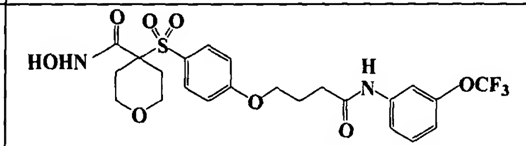
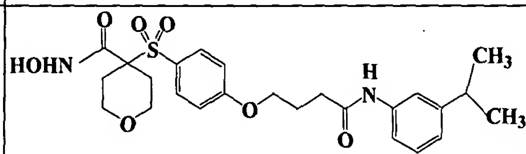
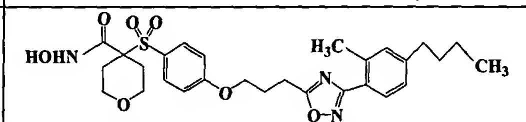
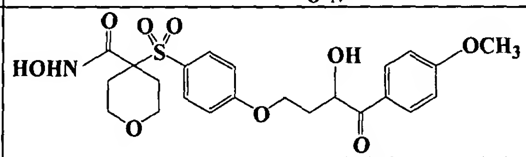
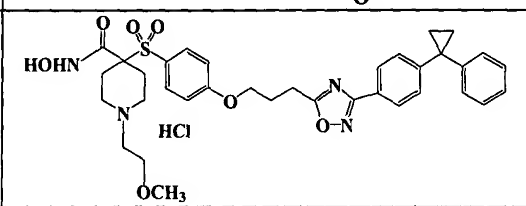
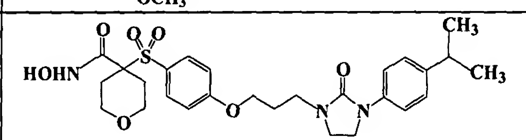
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
163		514.1700	514.1680	>10000 (>10000)	1370.7 (1010)	2880 (2500)	2.5 (11.6)	>10000 (>10000)
164		510.1950	510.1940	(>10000)	1073.2 (978)	(2720)	20.0 (6.85)	(>10000)
165		524.2107	524.2112	(>10000)	3396.2 (>10000)	(9750)	146.9 (144)	(>10000)

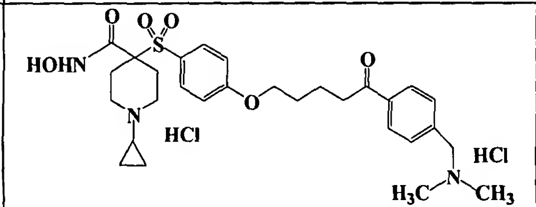
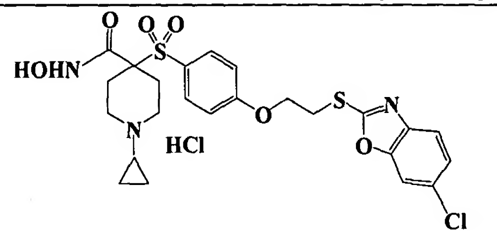
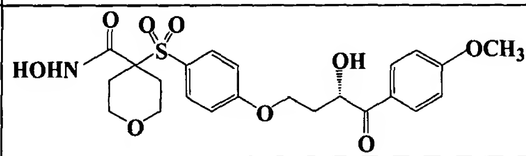
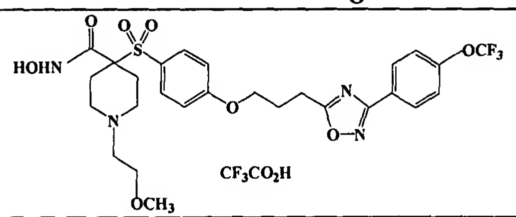
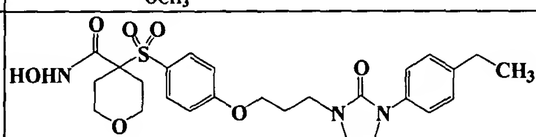
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
166		544.1561	644.1606	(>10000)	3081.7 (8090)	(8690)	135.9 (63.4)	(>10000)
167		540.2056	540.2029	(>10000)	3739.4 (128)	(68.1)	147.0 (78.9)	(>10000)
168		528.1856	528.1863	(>10000)	3428.2 (5500)	(6500)	34.3 (27.3)	(>10000)

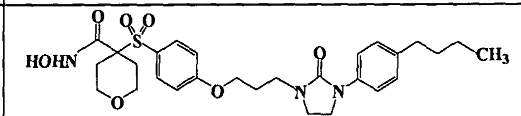
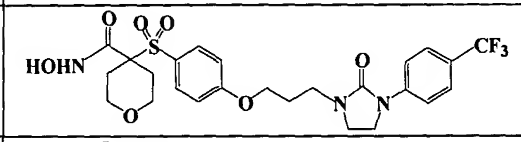
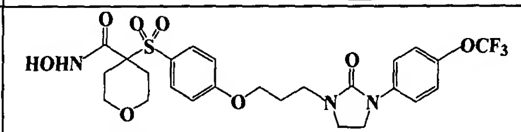
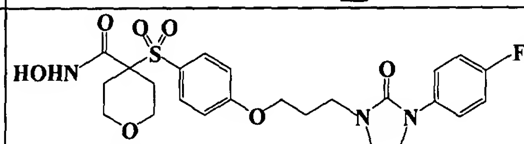
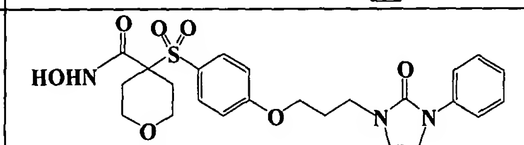
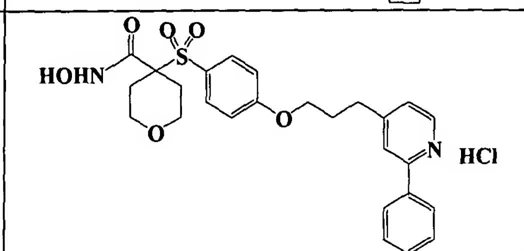
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
169		564.1014	564.1026	(>10000)	4363.5 (5360)	(6500)	70.7 (20.4)	(>10000)
170		532.1605	532.1618	(>10000)	1608.7 (1410)	(1500)	3.3 (6.79)	(>10000)
171		564.1014	564.1028	(>10000)	2288.8 (3190)	(6600)	62.8 (12.5)	(>10000)

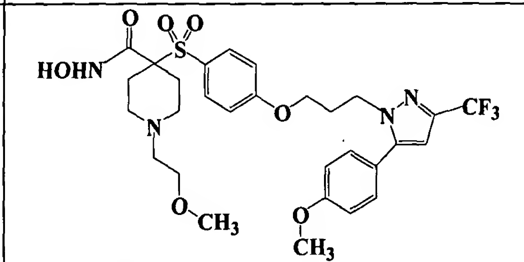
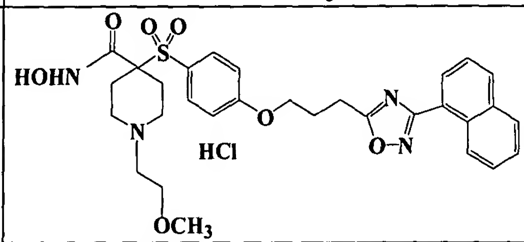
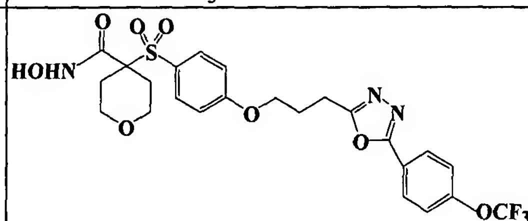
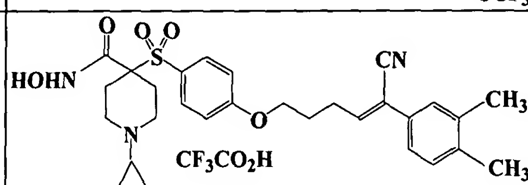
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
172		564.1014	564.1032	(>10000)	5163.1 (>10000)	(9440)	377.0 (71.1)	(>10000)
173		509.1950	509.1954	(>10000)	2120.4 (4090)	(3480)	12.2 (11.5)	(>10000)
174				>10000	708.6	4017	5.2	>10000
175		601.2696	601.2657	>10000 (>10000)	438.0 (872)	7296.6 (1390)	1.4 (2.01)	>10000 (>10000)

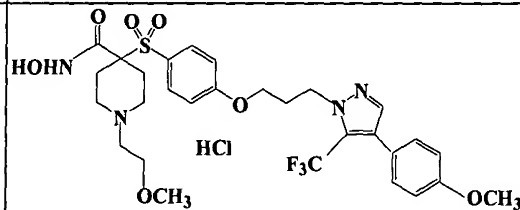
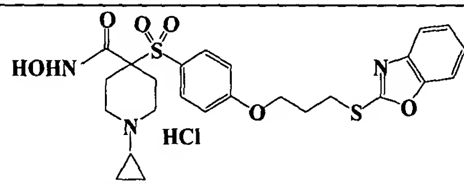
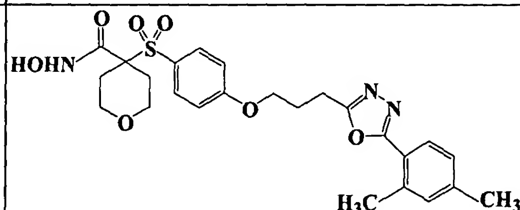
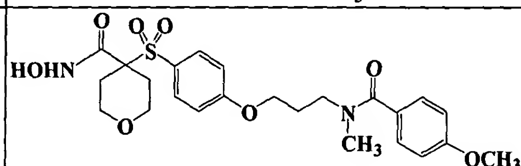
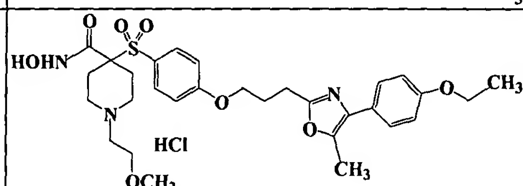
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
176					108.9		7.8	
177					333.2		17.0	
178				>10000 (>10000)	28.4 (39.3)	1166.4 (306)	7.8 (1.71)	>10000 (>10000)
179					246.9		1.1	
180					443.0		17.0	

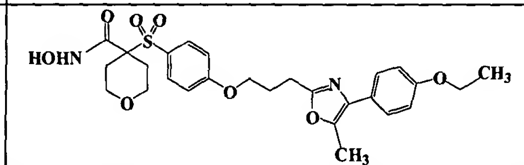
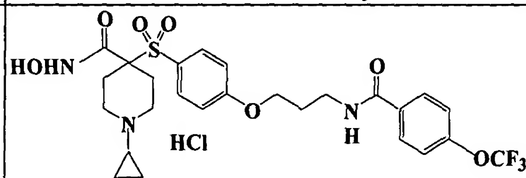
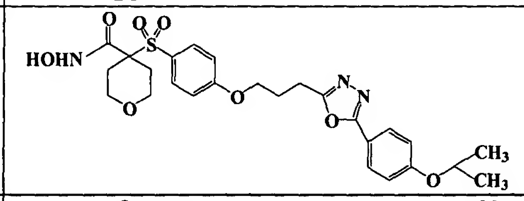
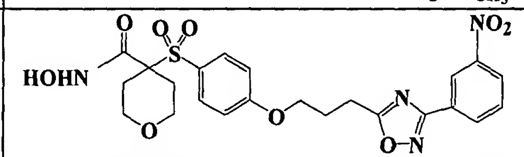
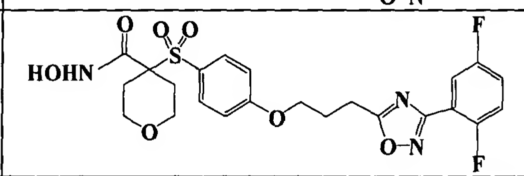
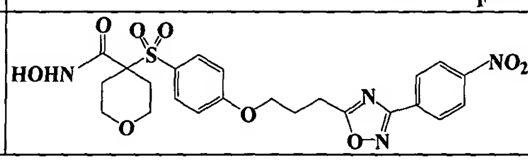
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
181				>10000 (1850)	13.9 (15.8)	26.4 (40.5)	0.3 (0.27)	8059 (4830)
182				>10000 (6540)	33.1 (34.3)	62.1 (85.4)	0.5 (0.212)	>10000 (5850)
183				(>10000)	708.0 (643)	(2510)	21.0 (15.1)	(>10000)
184				1528.7	30.4	103.5	3.9	2715.4
185				(>10000)	84.7 (116)	(220)	12.4 (3.73)	(>10000)
186					609.9		13.5	

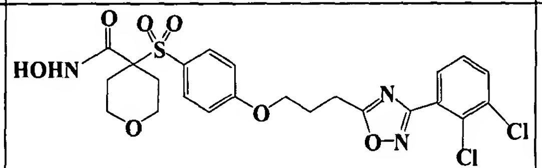
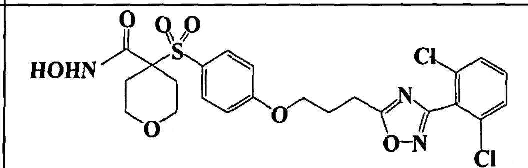
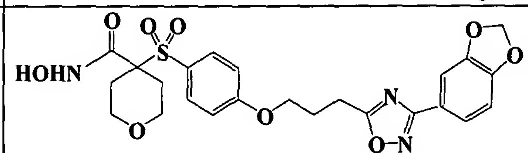
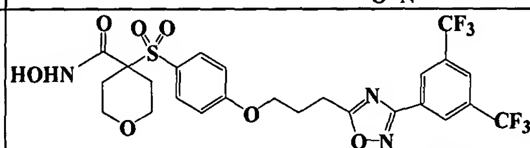
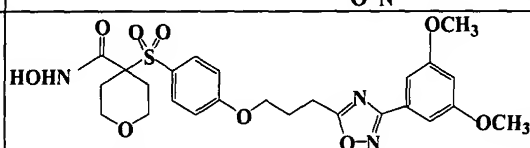
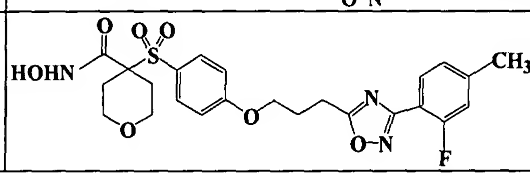
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
187				3868	3.6	11.2	1.8	1425
188				>10000	4.7	48.2	0.3	3537.7
189				1070	19.3	24.1	1.9	4316
190				>10000 (>10000)	165.9 (283)	1742.6 (669)	0.5 (0.6)	>10000 (>10000)
191				6956	341.2	383.4	9.5	>10000

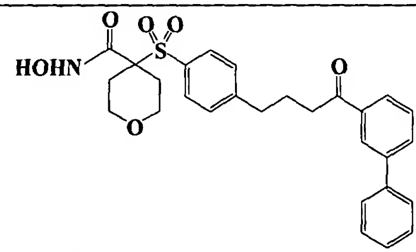
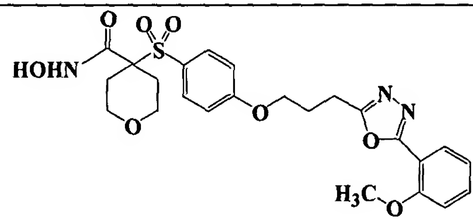
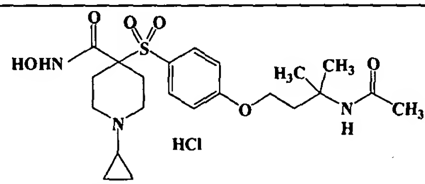
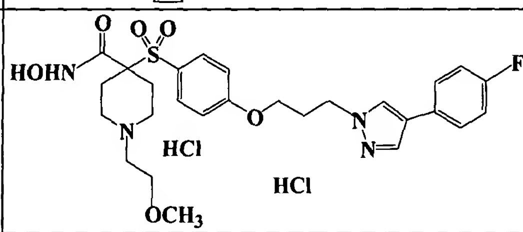
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
192					1256.4		15.4	
193				5931.6	312.3	272.5	6.8	>10000
194				>10000	221.6	515.7	6.2	>10000
195				4381.7	20.6	45.8	7.5	2741.5
196					32.2		11.4	
197				>10000 (>10000)	13.2 (30.7)	432.2 (334)	0.5 (0.37)	>10000 (>10000)

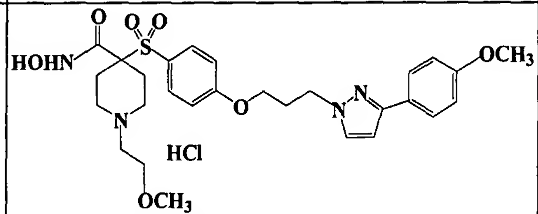
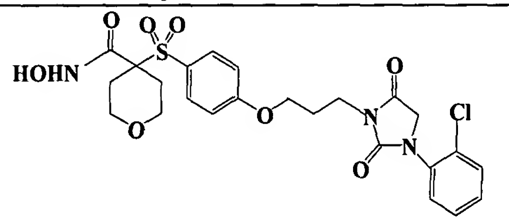
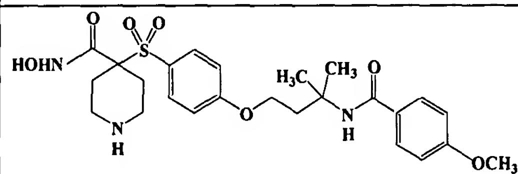
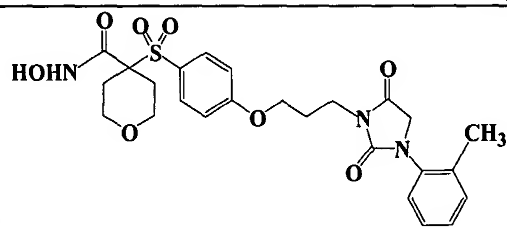
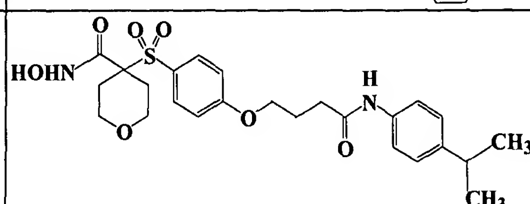
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
198					4527.4		834.9	
199				(>10000)	133.2 (228)	(59.5)	7.4 (3.09)	(>10000)
200				7498	84.0	1207.2	0.6	>10000
201		538.2376	538.2362	>10000	127.7	4509.5	0.7	>10000

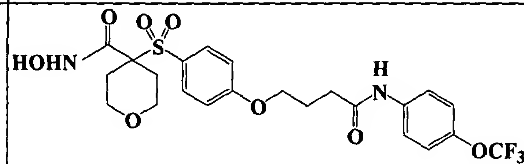
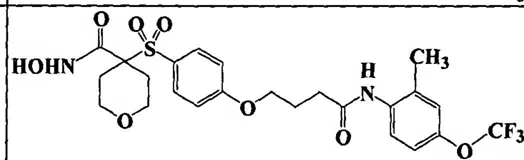
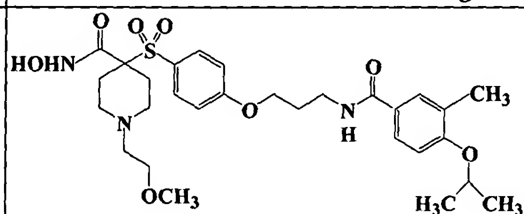
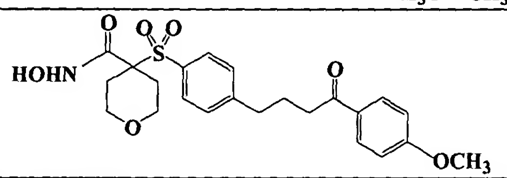
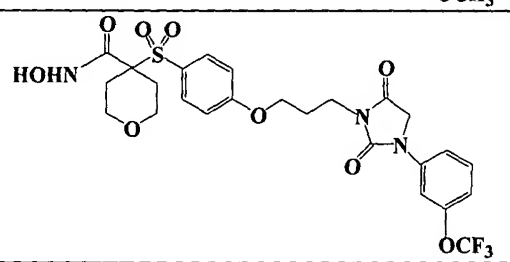
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
202					1604.4		41.9	
203				>10000	4.2	6.0	1.0	>10000
204				>10000	145.7	1824.8	0.6	>10000
205					4780.2		17.6	
206				>10000	92.6	59.4	15.8	3112

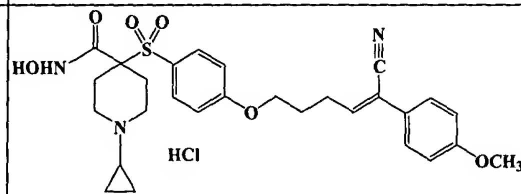
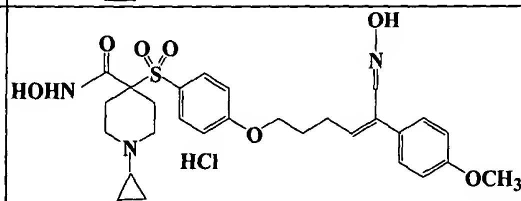
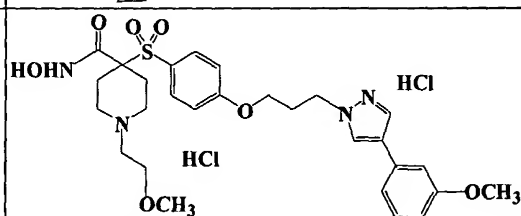
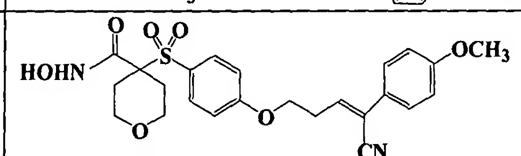
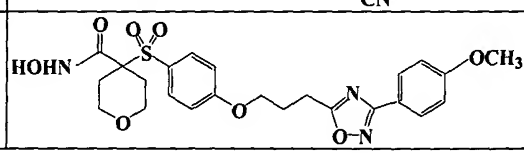
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
207				>10000	114.3	126.7	3.7	>10000
208				>10000	230.2	6587.6	0.6	>10000
209				>10000	172.5	905.6	1.4	>10000
210				>10000	6.9	284.6	1.3	>10000
211				9653	26.2	863.5	0.4	>10000
212				1408	4.1	212.2	0.3	>10000

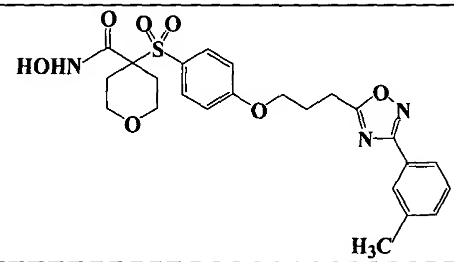
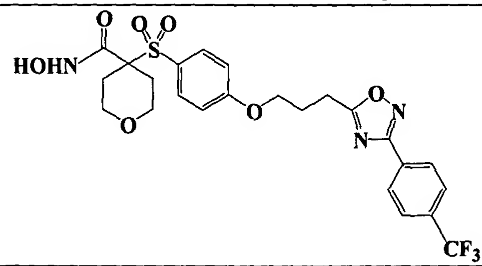
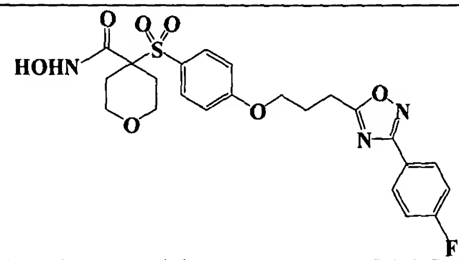
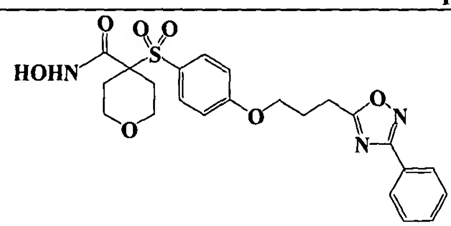
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
213				>10000	54.8	2204	2.2	>10000
214				>10000	15.8	4239	3.3	>10000
215				>10000	20.3	767.9	0.3	>10000
216					1952.2		51.2	
217				>10000	48.9	5179	4.6	>10000
218				>10000	40.4	2973	1.4	>10000

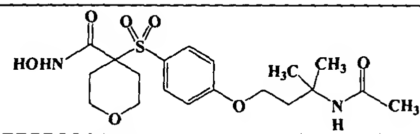
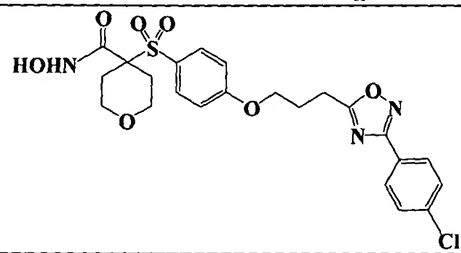
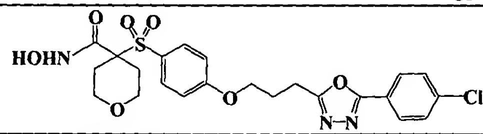
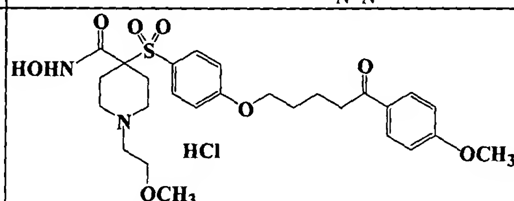
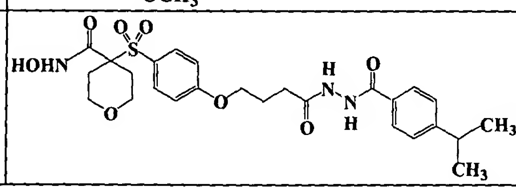
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
219				>10000 (5600)	60.8 (105)	77.7 (59.5)	0.4 (0.355)	>10000 (7940)
220				>10000	409.7	1466.8	5.7	>10000
221					8796.4		243.8	
222					138.1		13.3	

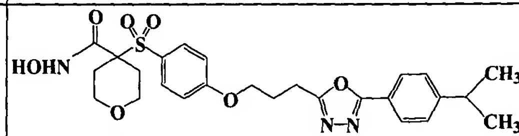
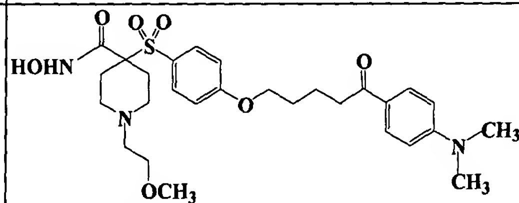
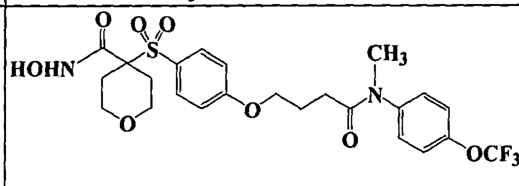
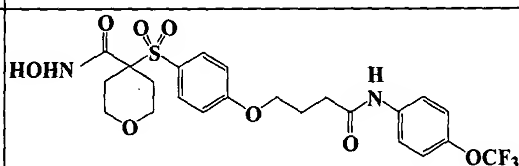
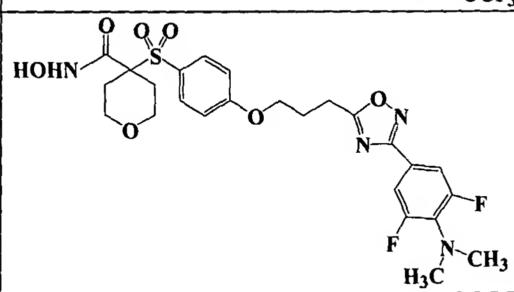
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
223					69.7		11.9	
224				>10000	193.5	1466.8	4.7	>10000
225					2332.3		17.8	
226				>10000	222.0	2144.0	4.3	>10000
227					2.7		0.2	

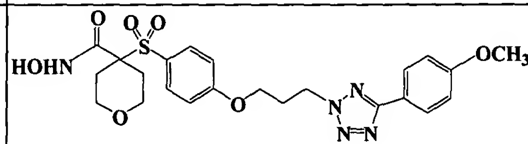
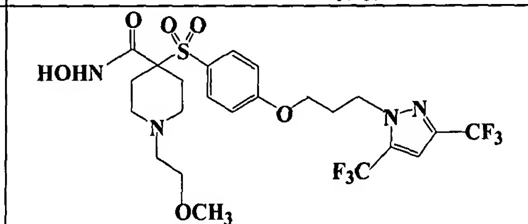
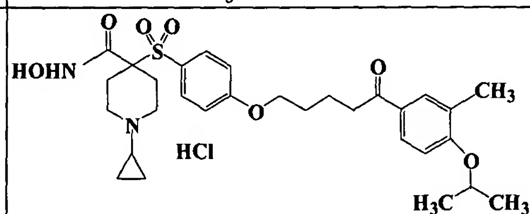
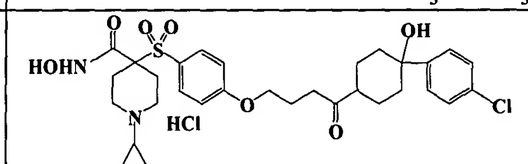
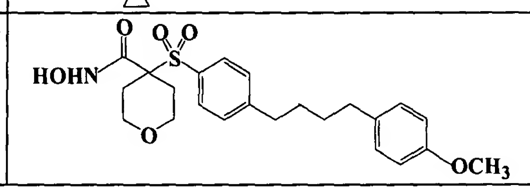
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
228				6871 (3940)	11.4 (22.4)	180.4 (247)	0.2 (0.324)	>10000 (6290)
229				5033 (955)	12.2 (10.4)	293.7 (281)	1.7 (0.27)	>10000 (7870)
230				>10000	555.2	1017.7	1.1	>10000
231				>10000	1.6	10.2	0.2	641.7
232				>10000	74.2	877.7	5.6	>10000

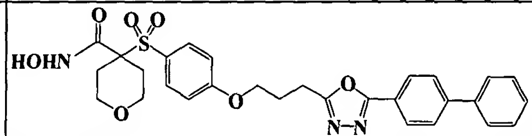
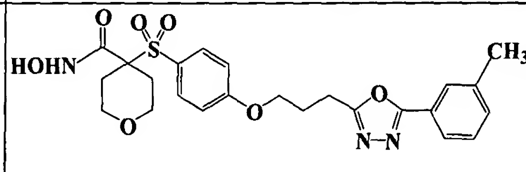
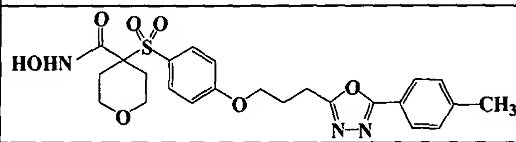
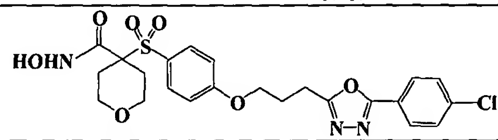
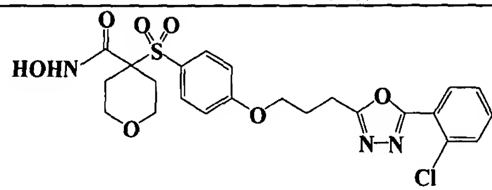
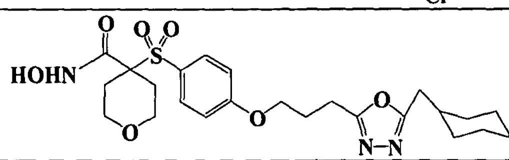
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
233				>10000 (>10000)	25.5 (60.18)	831.8 (509.42)	0.1 (0.137)	>10000 (>10000)
234		596.2430	596.2441		213.4		10.3	
235					421.7		26.0	
236					7.6		3.4	
237				>10000	42.5	1111	0.7	>10000

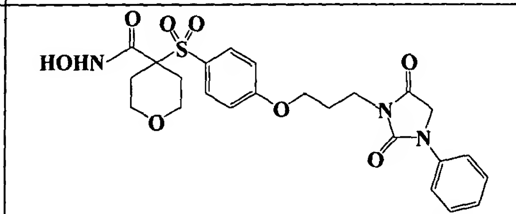
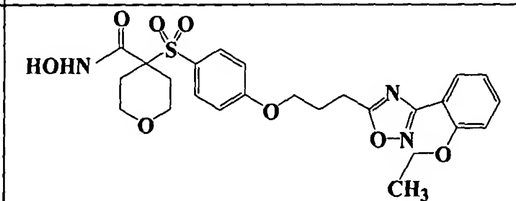
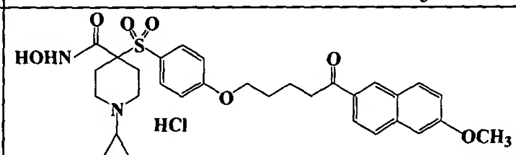
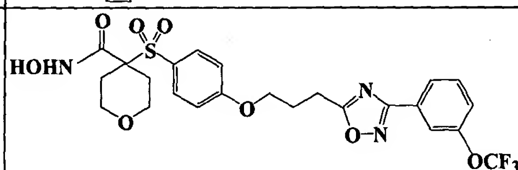
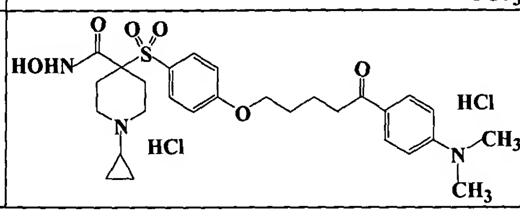
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
238				>10000	78.7	1186.1	1.2	>10000
239					236.9		2.5	
240				>10000	84.0	1428.4	0.7	>10000
241				>10000	60.2	944.2	1.3	>10000

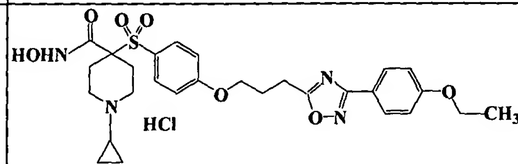
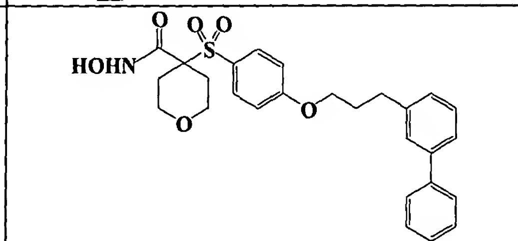
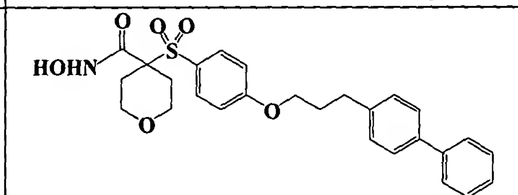
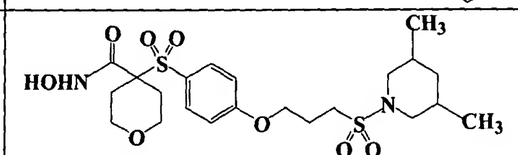
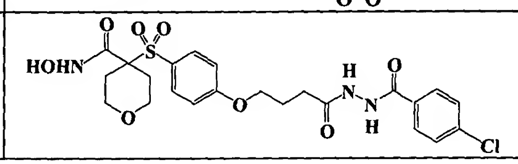
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
242					2720.2		203.0	
243				9313.6	49.4	2101.9	0.5	>10000
244				3250.6	18.8	108.2	0.7	>10000
245				>10000	8.6	61.1	0.2	>10000
246				1166.7	7.5	104.7	3.0	>10000

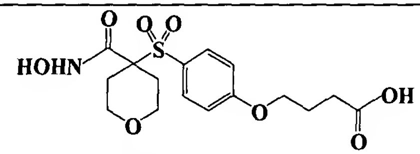
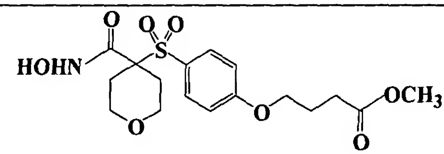
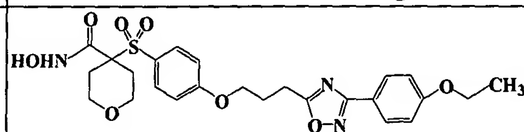
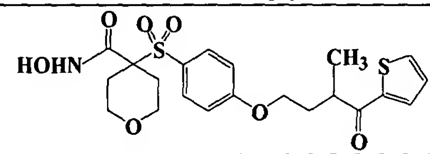
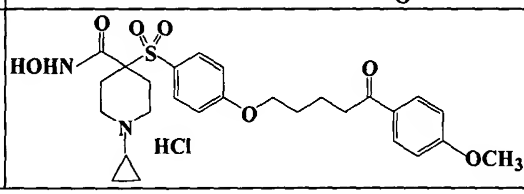
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
247				3610.8	445.1	341.1	1.1	>10000
248				>10000	15.7	105.6	0.2	1704.1
249				>10000 (>10000)	226 (333)	3628.6 (1490)	5.09 (1.49)	>10000 (>10000)
250				4406.1 (1440)	2.5 (3.12)	22.5 (12.5)	0.3 (0.127)	7630.2 (1700)
251					182.4		5.4	

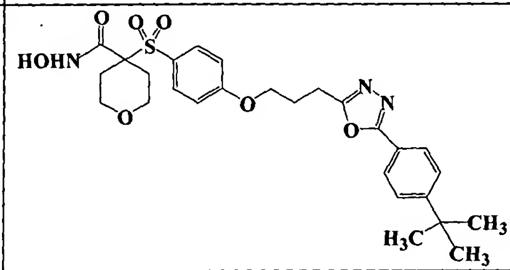
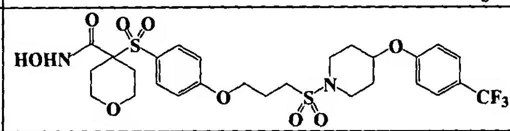
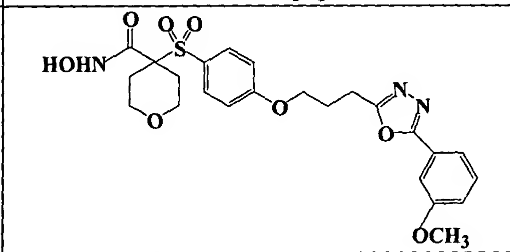
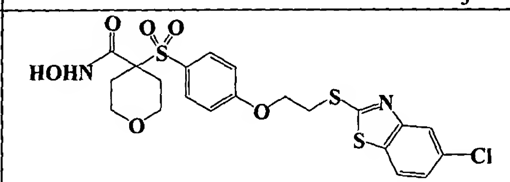
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
252				5602.7	47.9	1052.4	0.2	>10000
253					1448.2		32.4	
254				>10000	138.3	968.2	1.7	>10000
255					51.3		1.9	
256				>10000	0.1	37.9	<0.1	>10000

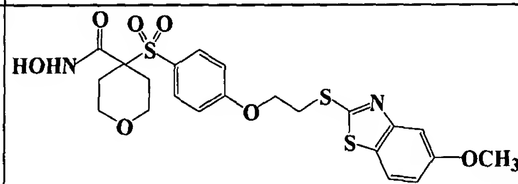
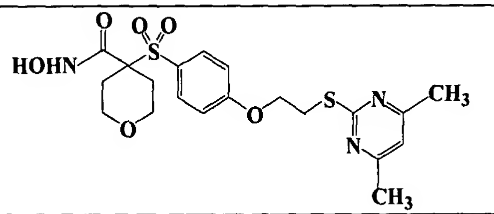
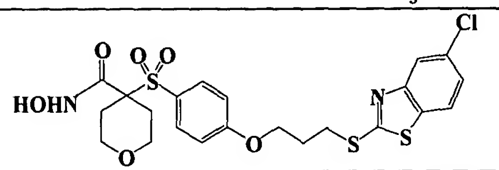
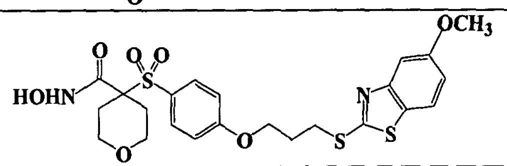
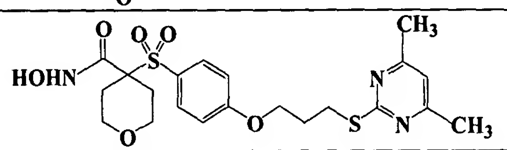
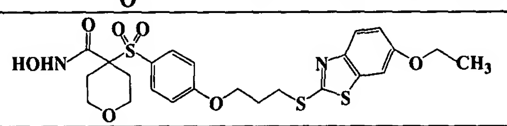
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
257				>10000	173.8	6227	0.5	>10000
258				>10000	173.5	1956	1.7	>10000
259				7256	201.1	1876	0.7	>10000
260				1159	13.2	391.0	1.8	>10000
261				>10000	178.3	1185.0	1.9	>10000
262				>10000	118.3	1702.3	3.0	>10000

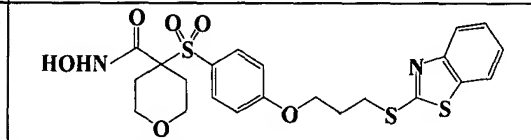
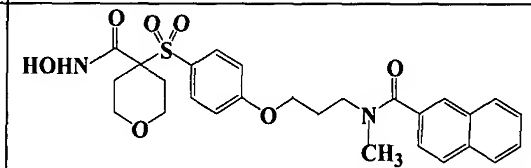
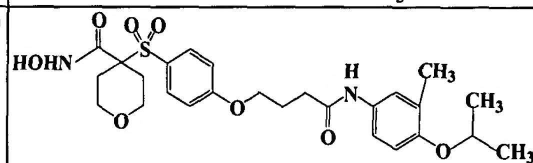
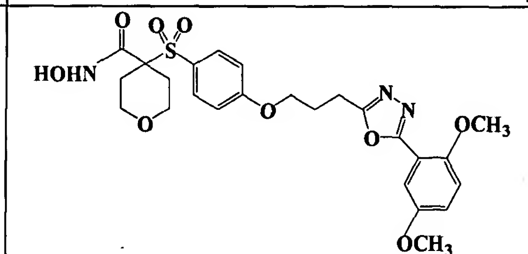
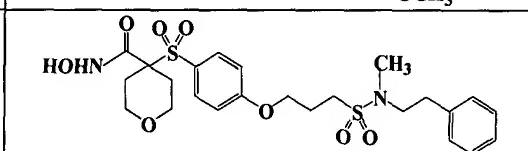
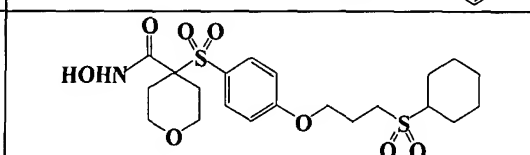
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
263				>10000	87.7	3267.5	3.8	>10000
264				>10000	162.8	287.1	5.3	>10000
265					40.0		0.2	
266				>10000	391.2	202.6	9.1	>10000
267				>10000	18.5	106.7		>10000

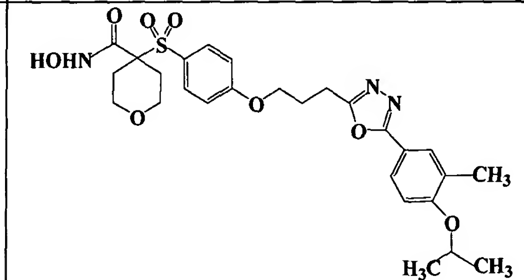
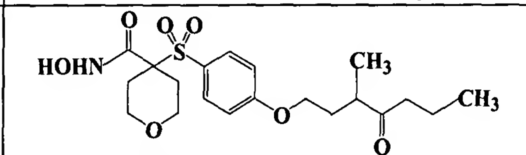
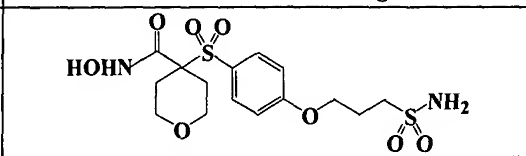
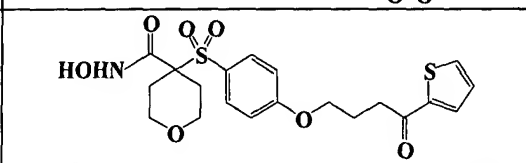
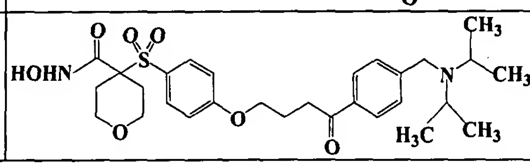
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
268				>10000	125.9	674.0	2.5	>10000
269				>10000	897.9	2755	1.8	>10000
270					521.8		8.1	
271				>10000	8.7	531.8	2.9	>10000
272				399	4.2	152.1	2.8	>10000

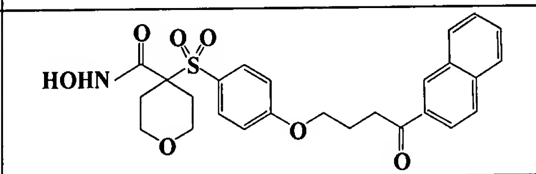
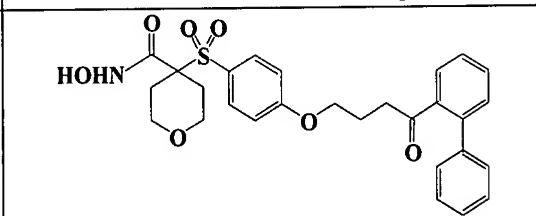
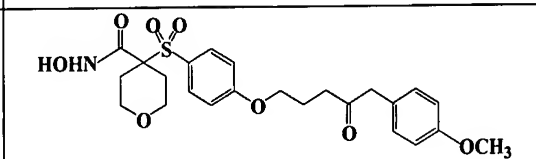
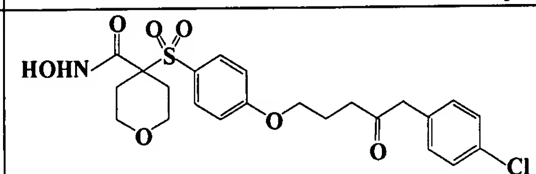
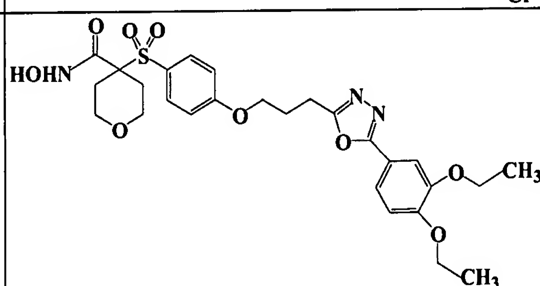
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
273		405.1332	405.1335		1010.7		304.0	
274		402.1223	402.1225	9864	15.4	33.6	4.1	>10000
275					115.2		1.7	
276				6670.4	17.4	196.3	2.8	7019.9
277				>10000	3.5	41.5	0.2	>10000

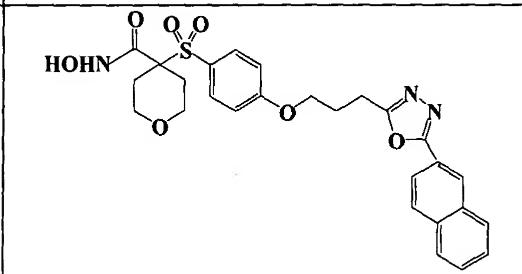
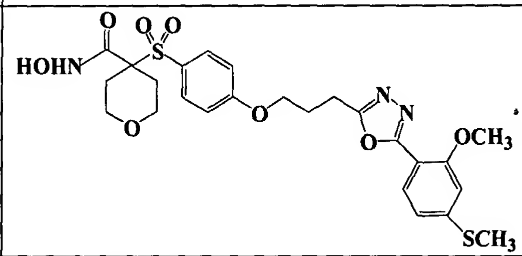
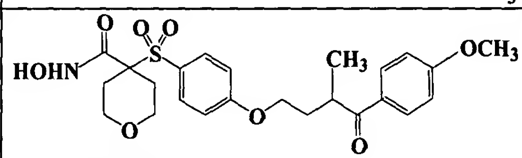
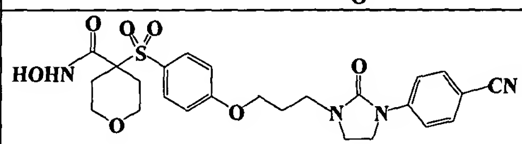
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
278		544.2117	544.2104	>10000	207.9	494	3.7	>10000
279					15.9		9.4	
280		518.1597	518.1578	>10000	170.1	2034	1.5	>10000
281		529.0329	529.0353	>10000	70.4	276.1	1.3	>10000

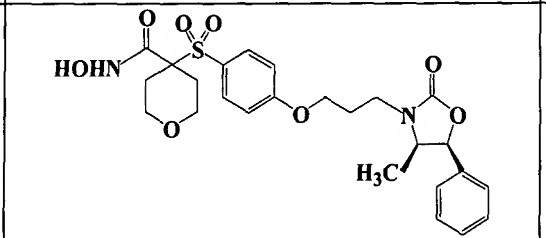
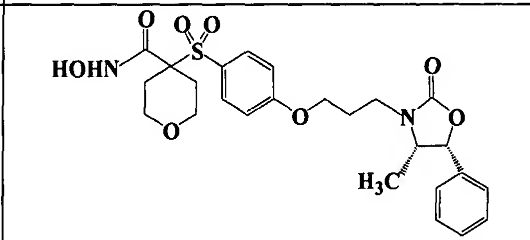
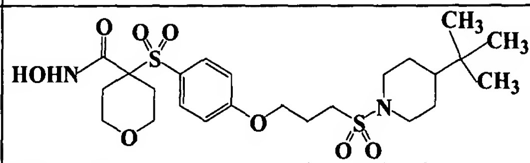
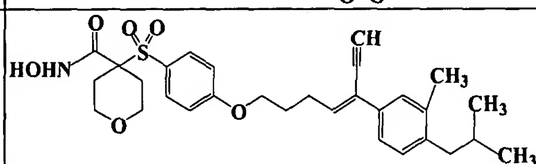
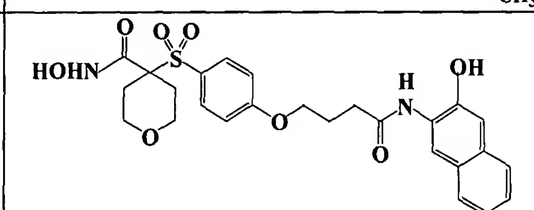
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
282		525.0824	525.0827	>10000	43.3	704.3	2.6	>10000
283		468.1263	468.1257		186.2		29.3	
284		543.0485	543.0500	>10000	10.1	18.5	1.1	>10000
285		539.0980	539.0978	>10000	16.7	23.6	1.8	>10000
286		482.1420	482.1421	>10000	74.9	1134.5	4.0	>10000
287		553.1137	553.1137	>10000	3.6	16.4	0.8	>10000

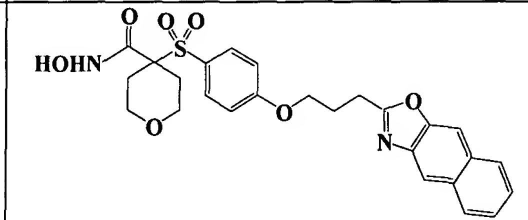
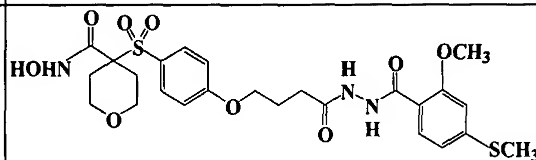
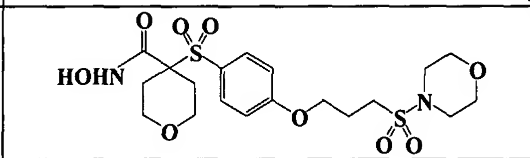
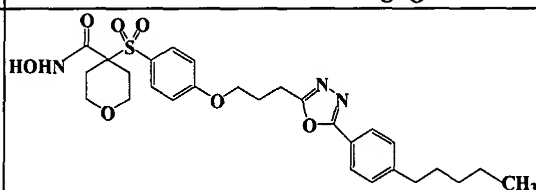
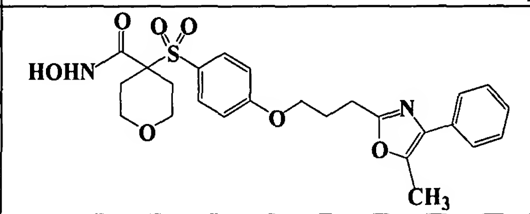
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
288		509.0875	509.0880	>10000	2.3	10.6	0.8	>10000
289		527.1852	527.1838	>10000	2720.2	>10000	10.1	>10000
290				>10000 (>10000)	590.2 (1009.04)	>10000 (>10000)	1.1 (0.547)	>10000 (>10000)
291					100		8.0	
292				970	14.4	163.5	2.4	>10000
293				6147	2.3	447.9	2.6	>10000

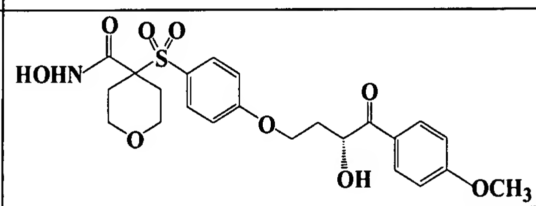
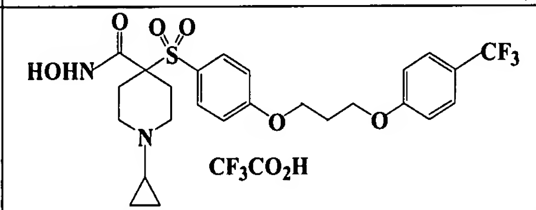
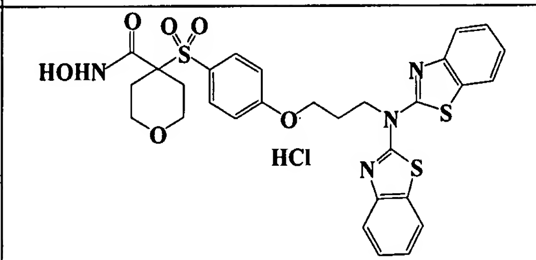
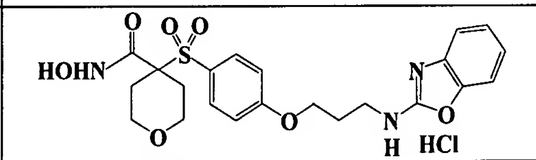
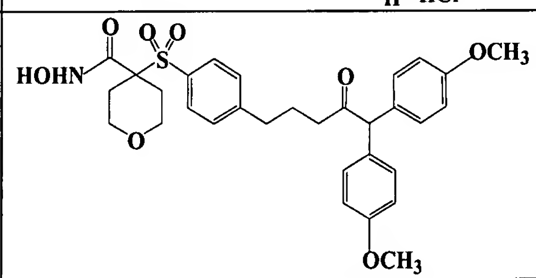
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
294				4623	100.0	447.9	4.3	>10000
295				>10000	15.6	172.1	2.6	>10000
296					1335.9		564.8	
297		454.0944	454.0986	6812	8.1	64.6	0.5	6562
298		561.2634	561.2641		11.9		18.1	

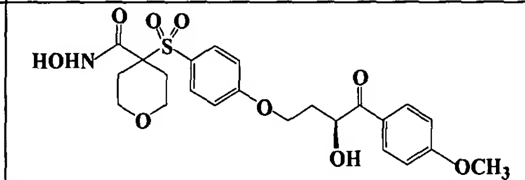
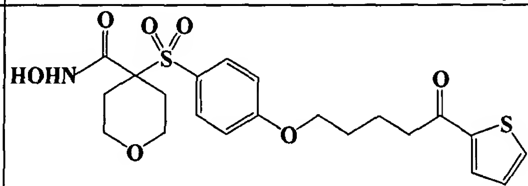
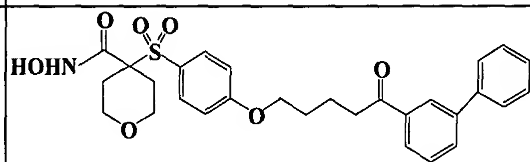
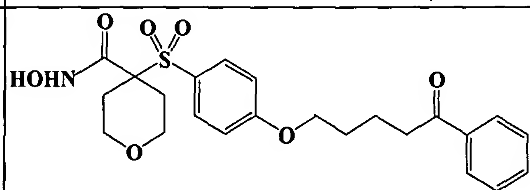
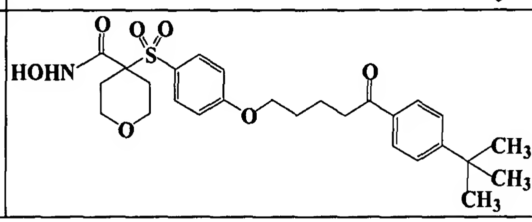
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
299		498.1586	498.1588		3.2		0.1	
300		524.1743	524.1729		12.5		6.7	
301		492.1692	492.1687	3655.3	0.2	9.1	<0.1	319.9
302		496.1197	496.1192	2728.9	0.2	2.9	0.1	94.9
303		576.2016	576.2198		50.0		9.9	

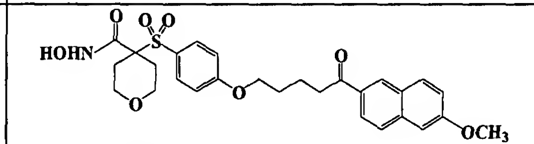
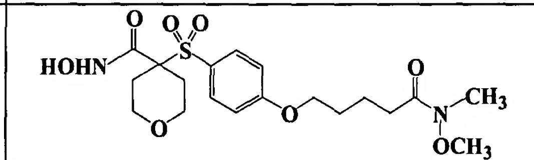
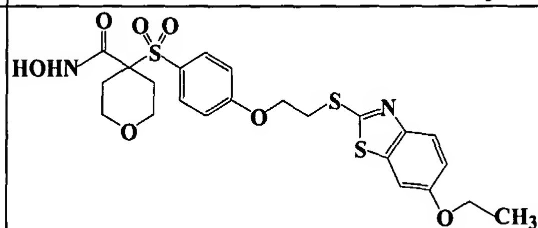
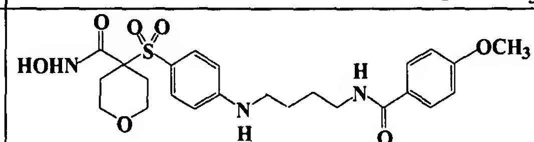
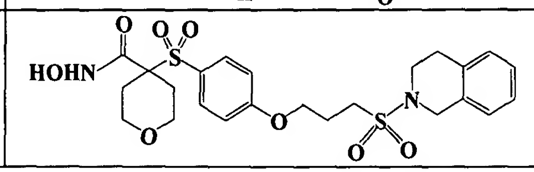
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
304		538.1648	538.1629		138.6		0.2	
305		569.1474	569.1444		175.9		3.9	
306				>10000	92.9	185.2	1.7	>10000
307				8135	135	139.5	4.5	>10000

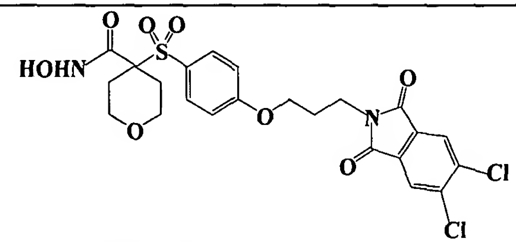
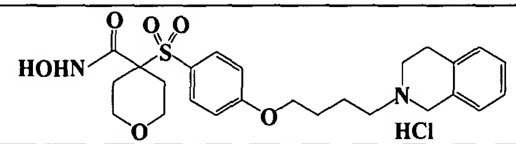
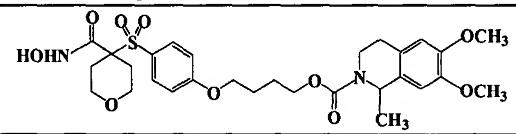
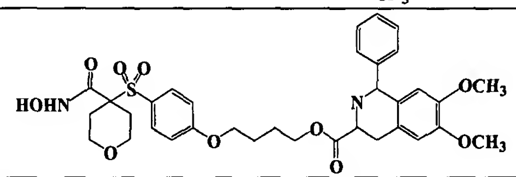
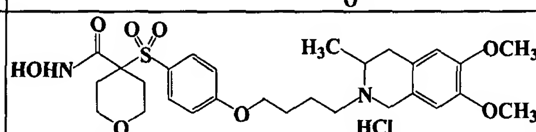
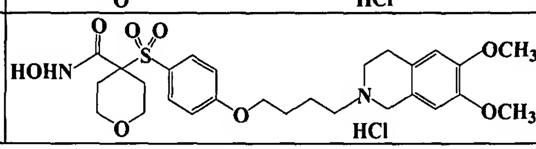
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
308		519.1801	519.1780	>10000	175.8	1601.1	3.7	>10000
309		519.1801	519.1772	>10000	135.3	1557.8	1.8	>10000
310				>10000	32.0	1980.5	3.0	>10000
311		543.2165	543.2165		25.6		2.6	
312		529.1645	529.1635		9.1		0.2	

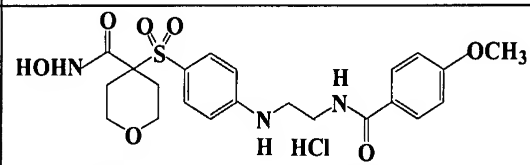
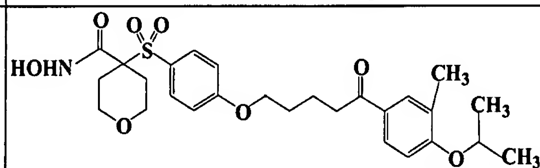
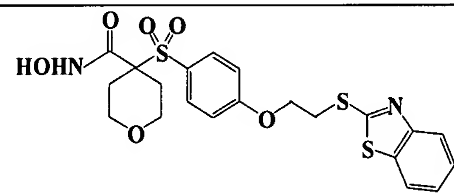
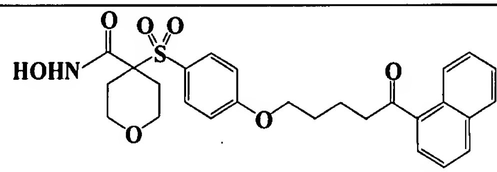
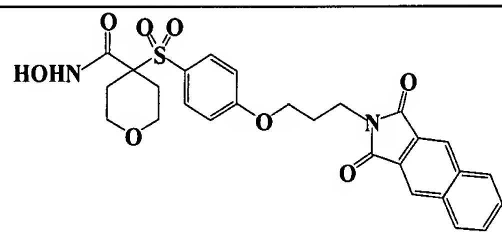
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
313		511.1539	511.1535		18.1		<0.1	
314					7.8		2.5	
315					12.8		12.7	
316		558.2274	558.2274	2678	2842	692.0	13.6	>10000
317		501.1695	501.1693	>10000	120.4	244.3	3.1	>10000

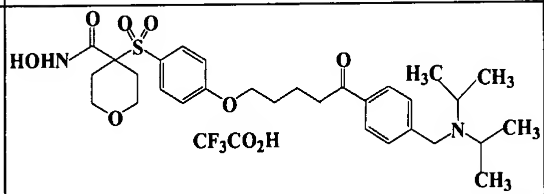
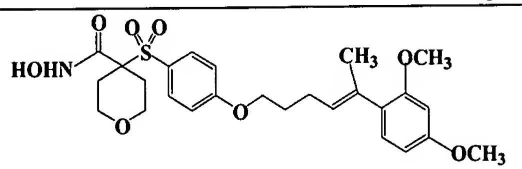
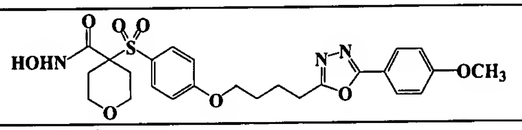
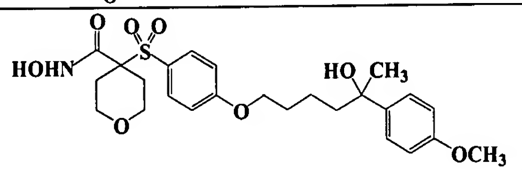
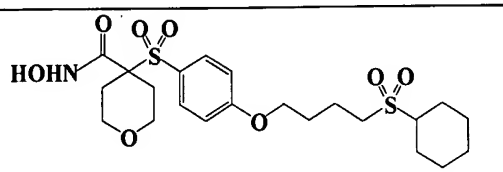
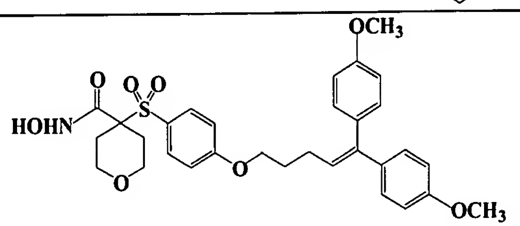
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
318					615		97.3	
319				>10000	5.8	258	1.0	4225
320					5864		6110	
321				>10000	1701	625.6	3.7	>10000
322		601.2220	601.2226		354		233	

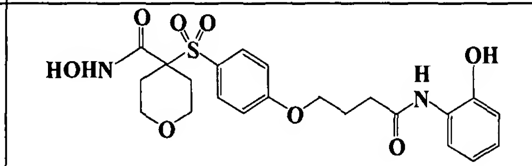
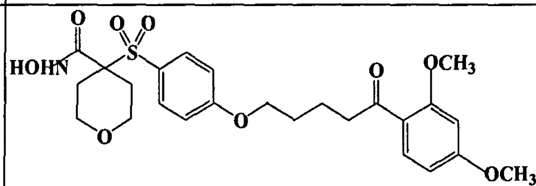
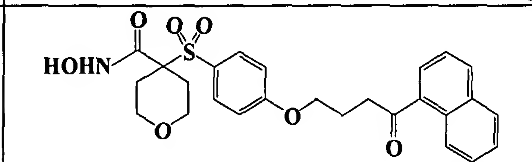
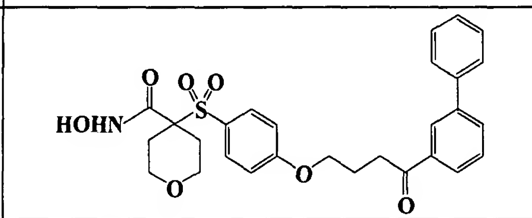
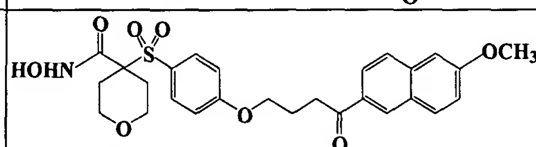
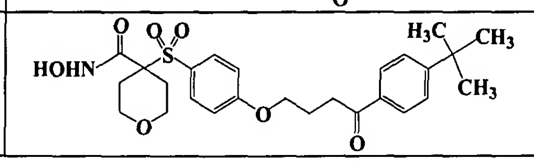
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
323					358.8		108	
324		468.1151	468.1148	2990	4.2	500	0.5	8002
325		538.1899	538.1918	>10000	11.0	4042	0.5	>10000
326		462.1586	462.1582	>10000	7.4	263	0.3	8316
327		518.2212	518.2203	>10000	50.7	5284	0.9	>10000

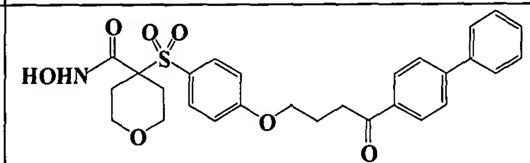
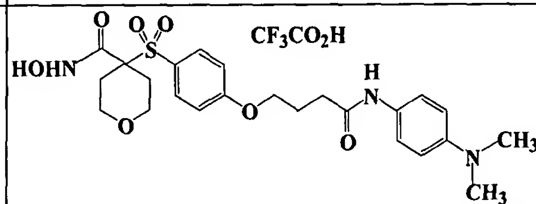
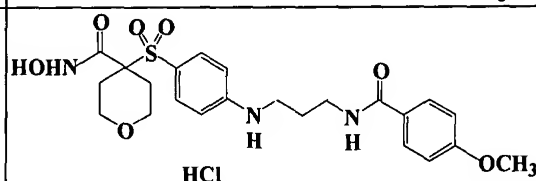
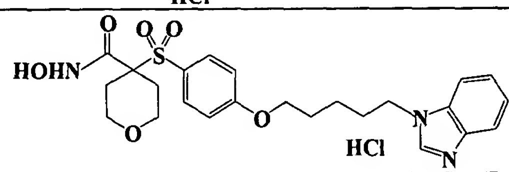
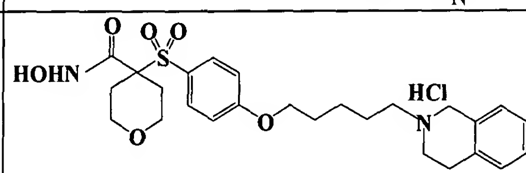
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
328		542.1849	542.1866		61.3		<0.1	
329					103.1		8.6	
330		539.0980	539.0985	>10000	261.7	216	16.0	592
331		506.1961	506.1954		386		261.4	
332				2459	3.6	132.4	2.6	>10000

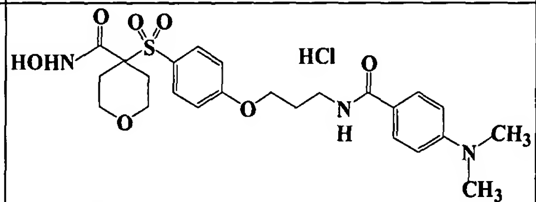
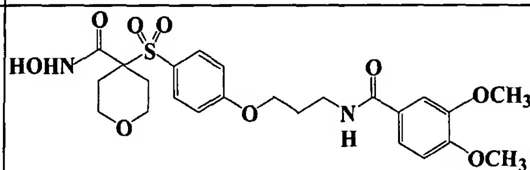
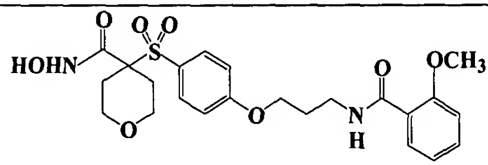
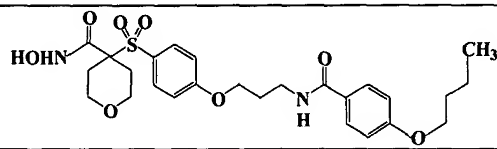
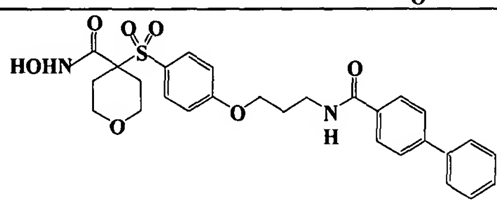
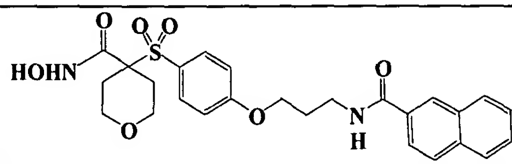
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
333		557.0552	557.0562	>10000	656.3	3240	1.8	>10000
334		489.2059	489.2073	>10000	16.4	866	5.1	2876
335		607.2325	607.233	>10000	2.3	172.3	6.5	>10000
336		669.2482	669.2463		300.6		19.8	
337		563.2427	563.2414		41.9		12.2	
338		549.2271	549.2242		20.6		137.7	

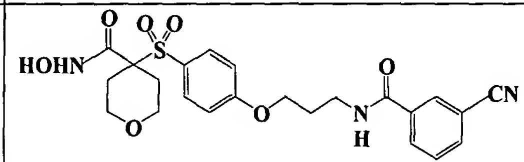
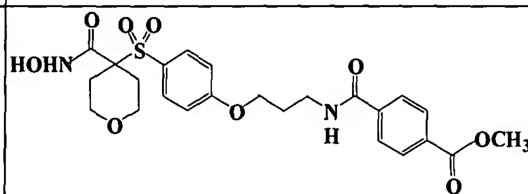
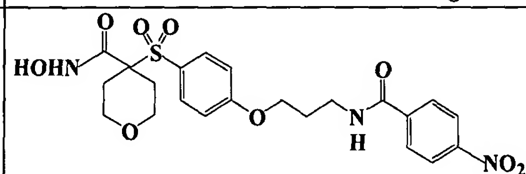
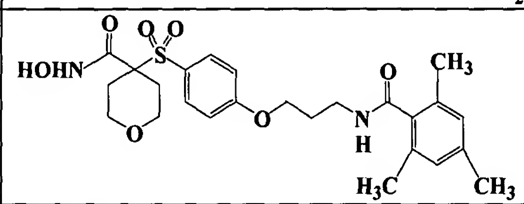
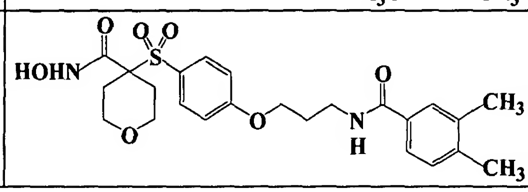
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
339		478.1648	478.1631		1205.8		932.9	
340		534.2162	534.2161	>10000	253.0	5590	1.9	>10000
341		495.0718	495.0689	>10000	16.8	1122	0.5	6400
342		512.1743	512.1769	>10000	41.2	2165	2.0	>10000
343					7702.4		2.4	

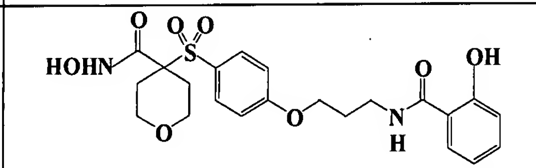
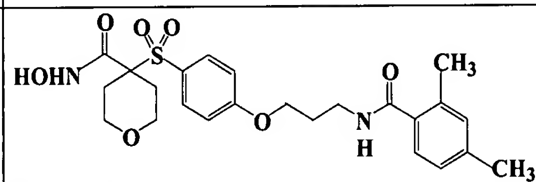
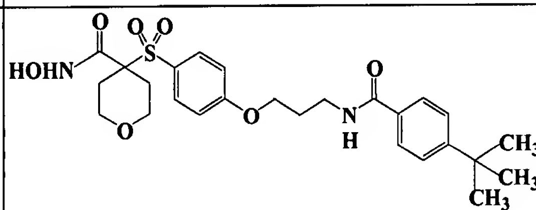
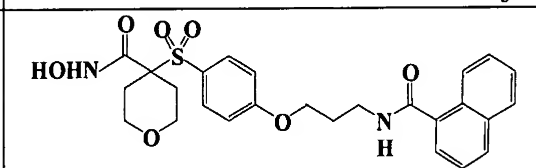
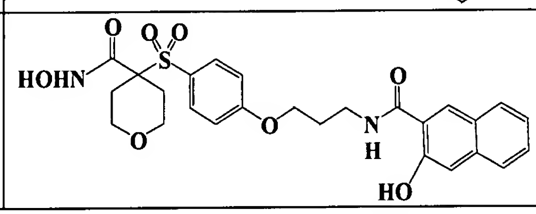
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
344		575.2791	575.2819		12.7		4.6	
345		520.2005	520.1988		271.1		14.3	
346		532.1754	532.171	>10000	2.6	2010	0.9	>10000
347					10.3		1.8	
348				>10000	61.8	>10000	4.4	>10000
349					505.3		39.0	

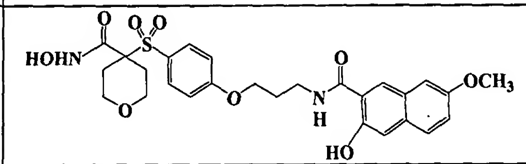
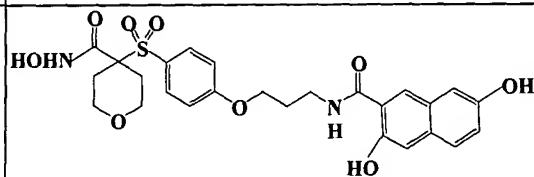
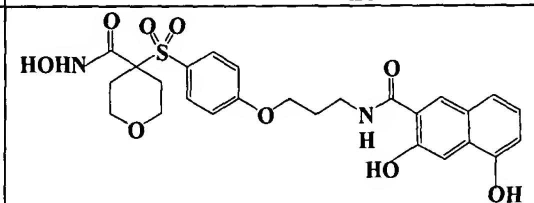
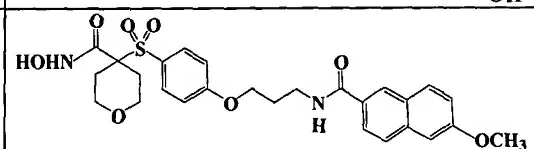
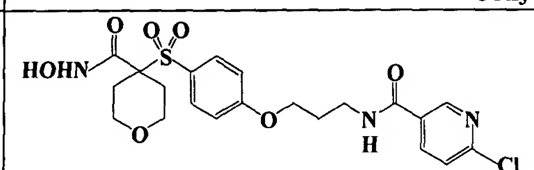
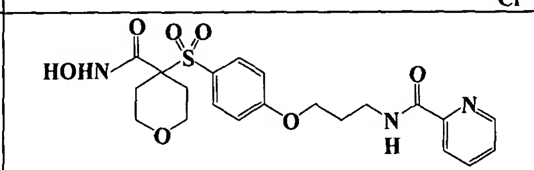
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
350		479.1488	479.1484	3283	2.6	271	0.5	2670
351		522.1798	522.1791	>10000	34.1	2225	1.0	>10000
352		498.1586	498.1576	>10000	33.6	3601	2.0	6238
353		524.1743	524.1703	>10000	25.1	1152	1.8	>10000
354		528.1692	528.1658					
355		504.2056	504.2017	>10000	17.4	1072	1.1	3622

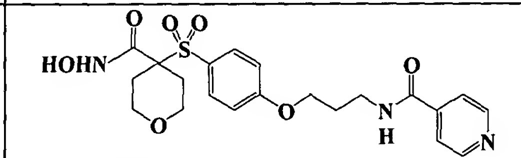
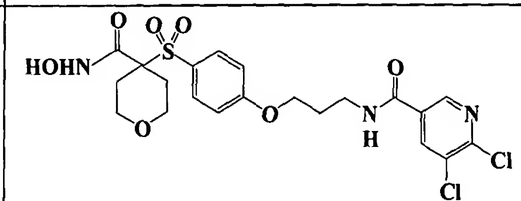
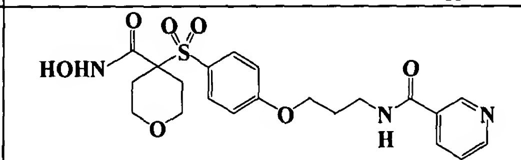
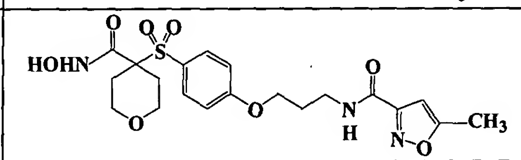
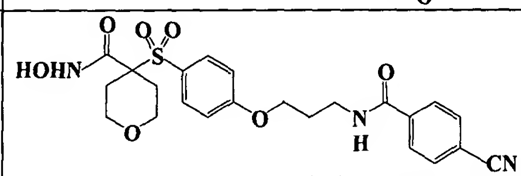
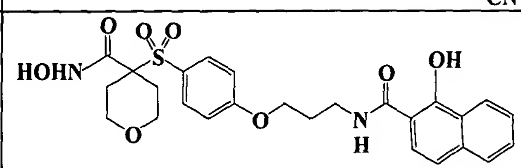
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
356		524.1743	524.1731	>10000	33.1	1650	0.8	>10000
357		506.1961	506.1964	>10000	10.2	952	1.7	>10000
358		492.1804	492.1813		768.4		14.6	
359		488.1855	488.1862	>10000	2.3	1183	1.0	7956
360		503.2216	503.2226	>10000	9.7	547	6.4	962

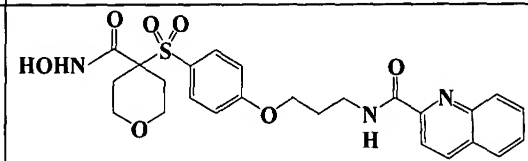
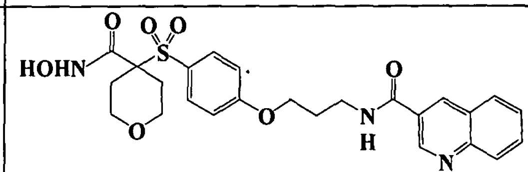
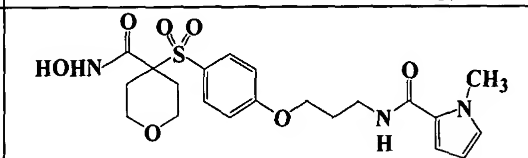
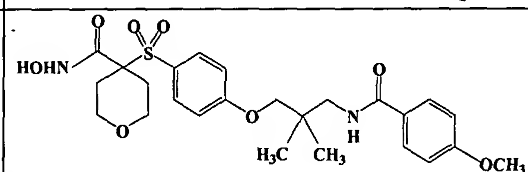
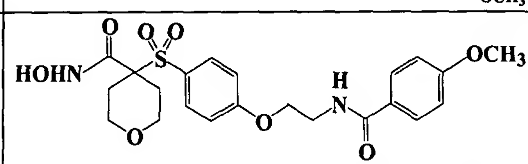
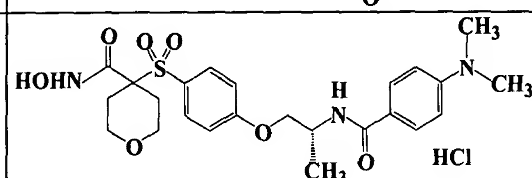
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
361		506.1961	516.1965	6000	500	>10000	0.5	>10000
362		523.1750	523.1763		347		3.7	
363		493.1645	493.1660		430		7	
364		535.2114	535.2105	>10000	250	>10000	1.8	>10000
365		539.1852	539.1846		21		0.6	
366		513.1695	513.1699		347		0.3	

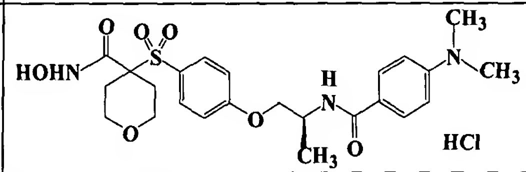
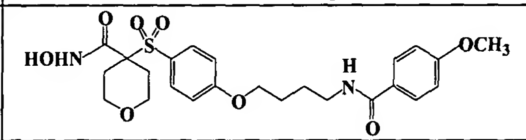
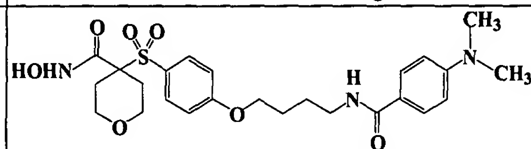
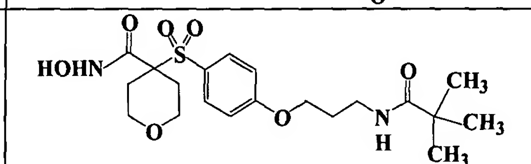
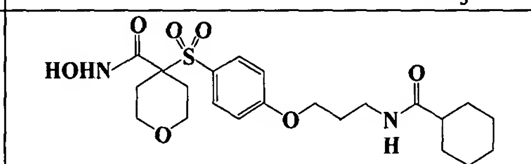
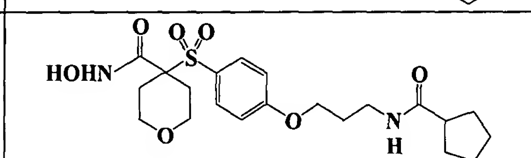
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
367		488.1491	488.1496		235		4.5	
368		521.1594	521.1594	>10000	150	9000	0.8	>10000
369		508.1390	508.1390		155		1.5	
370		505.2008	505.1990		900		37	
371		491.1852	491.1894	>10000	1100	9600	2.4	>10000

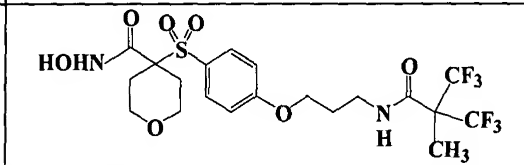
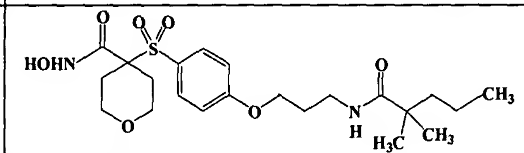
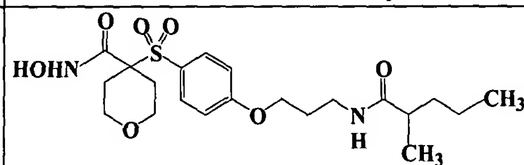
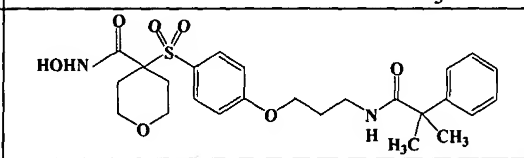
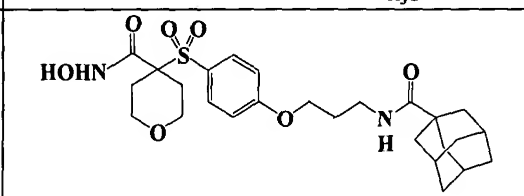
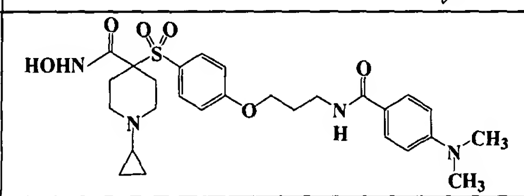
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
372		479.1488	479.1491		210		6	
373		491.1852	491.1843	>10000	940	3945	7	>10000
374		519.2165	519.2148		800		8	
375		513.1695	513.1695		425		17	
376		529.1645	529.1625	>10000	360	>10000	0.8	>10000

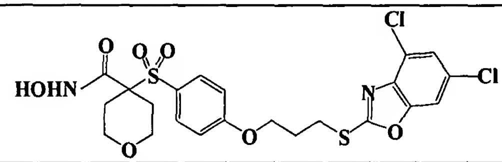
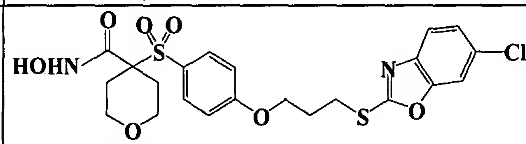
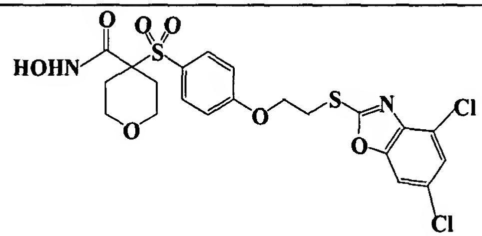
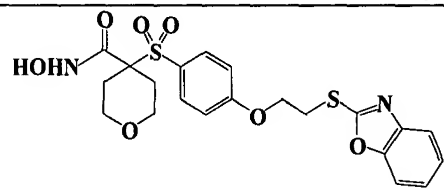
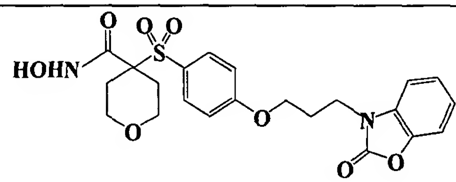
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
377		559.1750	559.1761		1271		5.9	
378		545.1594	545.1596		655		2.7	
379		545.1594	545.1585		258		10	
380		543.1801	543.1835		450		0.2	
381		498.1102	498.1090		193		1.4	
382		464.1491	464.1475		59		1.7	

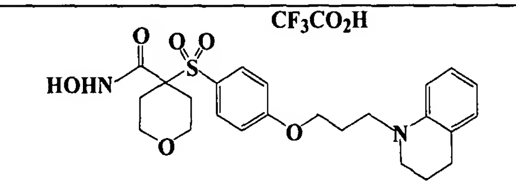
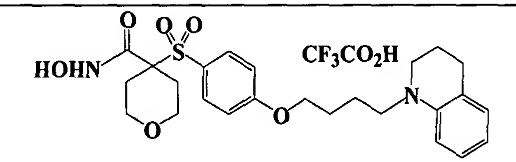
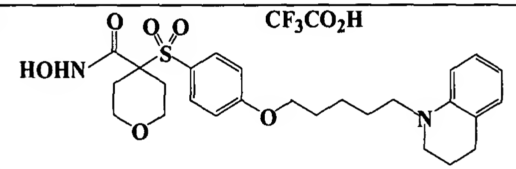
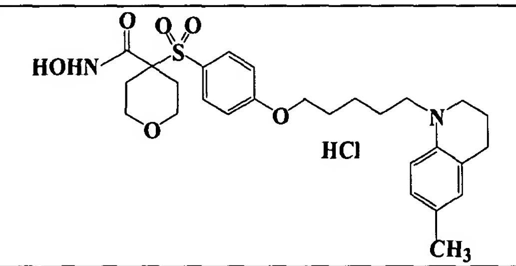
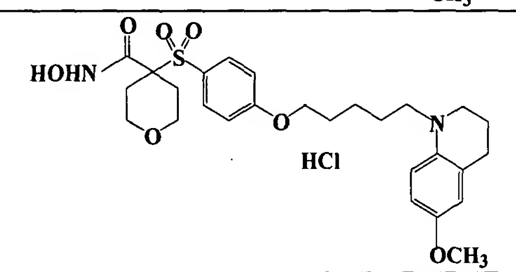
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
383		464.1491	464.1487		351		7.5	
384		532.0712	532.0709	>10000	176	2628	0.8	>10000
385		464.1491	464.1490	4341	253	>10000	3.3	>10000
386		468.1441	468.1459	>10000	131	35.3	1.2	9725
387		488.1491	488.1508		83		2.2	
388		529.1645	529.1640		185		2	

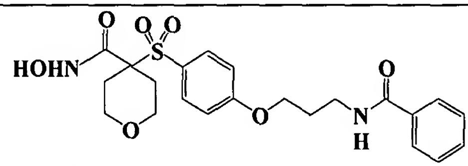
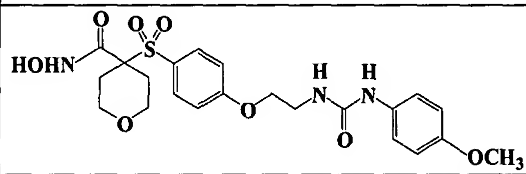
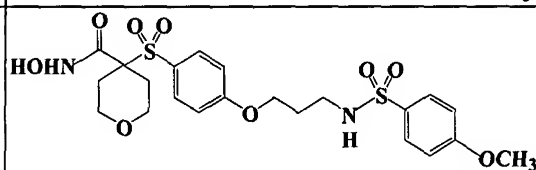
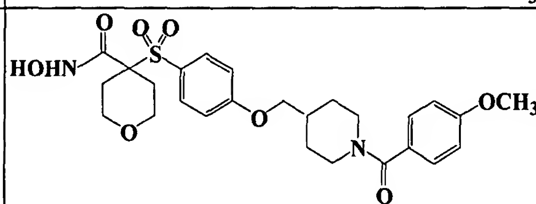
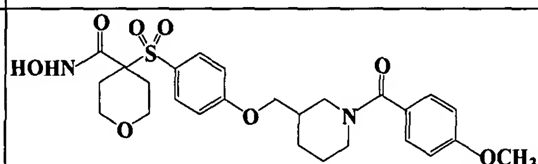
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
389		514.1648	514.1623		47		0.5	
390		514.1648	514.1641	>10000	907	>10000	2.7	>10000
391		466.1648	466.1647		900		7	
392		521.1958	521.1947	>10000	>10000	>10000	40	>10000
393		479.1488	479.1497		50		45	
394		506.1961	506.1961		3200		1900	

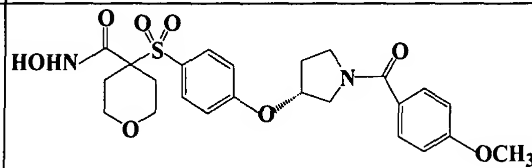
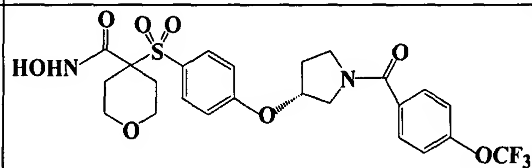
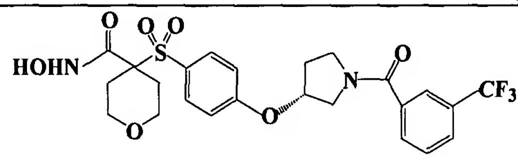
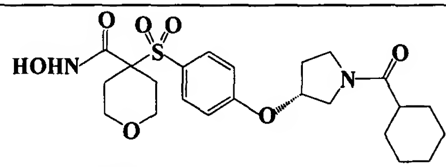
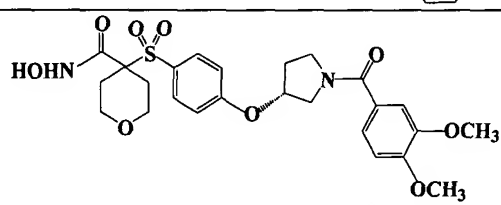
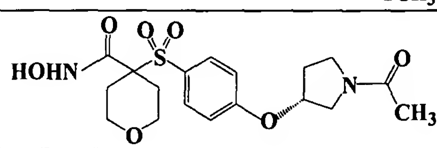
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
395		506.1961	506.1947		6000		305	
396		507.1801	507.1807		4		4	
397		520.2117	520.2093		3		14	
398		433	433		730		22	
399		469.2008	469.1988		650		8	
400		455.1852	455.1843		326		9	

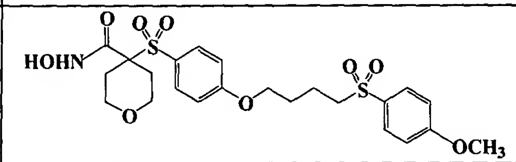
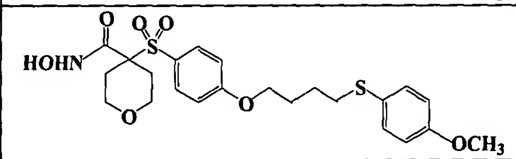
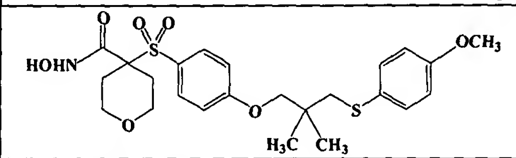
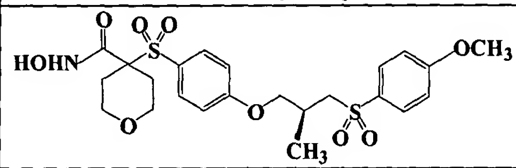
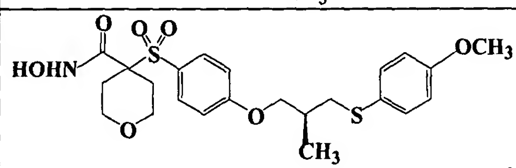
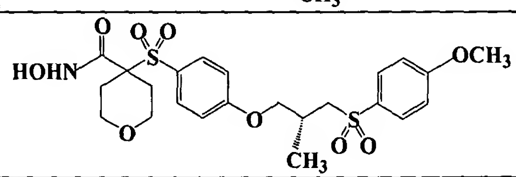
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
401		551.1287	551.1264		700		25	
402		471.2165	471.2144		454		30	
403		457.2008	457.1997	>10000	454	>10000	5.2	>10000
404		505.2008	505.1992		254		15	
405		521.5321	521.2323	>10000	2352	>10000	1.9	>10000
406		545.2434	545.2441	>10000	2200	>10000	4	>10000

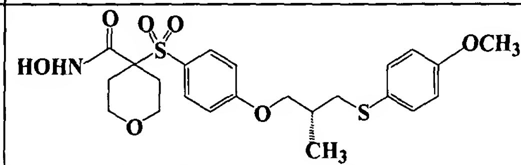
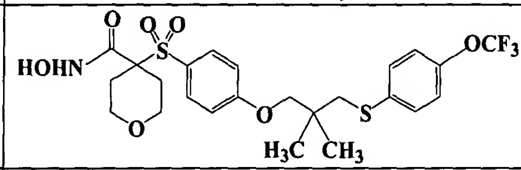
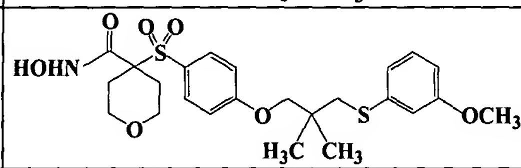
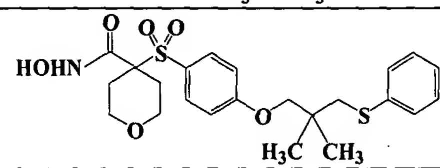
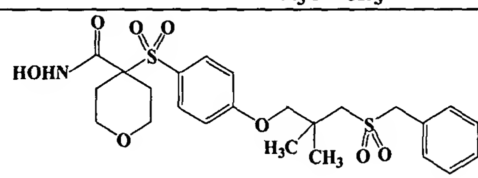
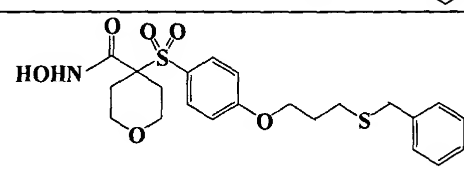
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
407		561.0324	561.0366		285		25	
408		527.0713	527.0694	>10000	90	49	2.5	6813
409		547.0167	547.0196	>10000	23	160	1	5644
410		479.0947	479.0978	4700	12	202	1.1	515
411		463.1175	463.1204	>10000	1517	>10000	587	>10000

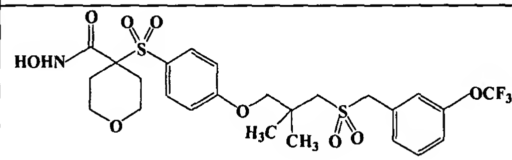
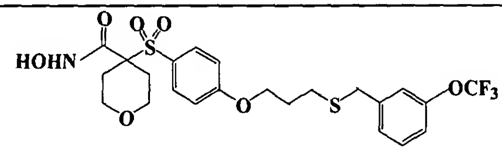
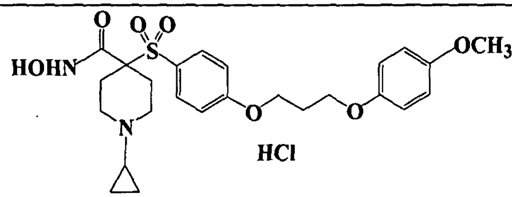
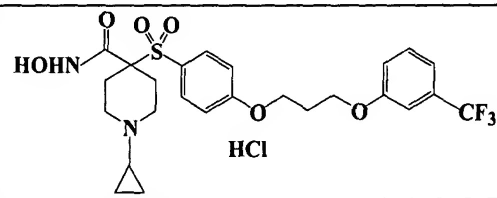
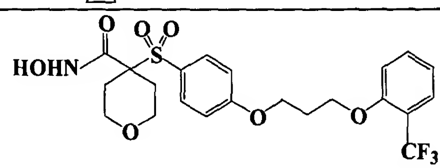
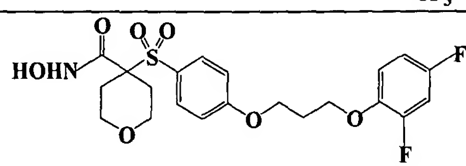
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
412		475.1903	475.0916		313		41	
413		489.2059	489.2068		61		8	
414		503.2216	503.2215		37		14	
415		517.2372	517.2377	>10000	51	1784	15	>10000
416		533.2321	533.2314		17		8.6	

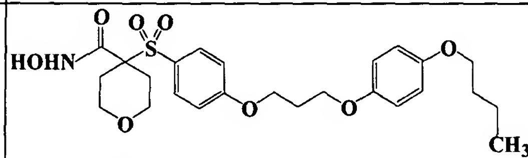
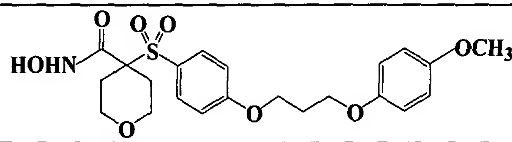
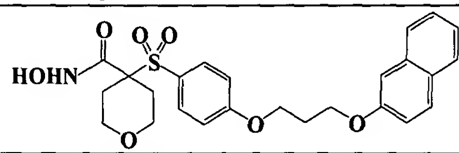
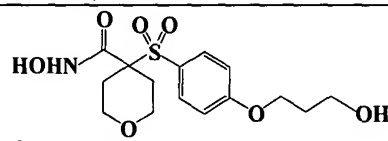
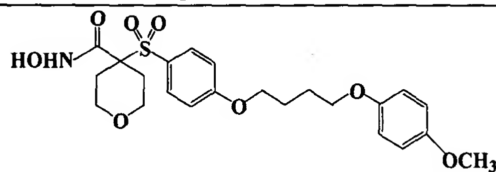
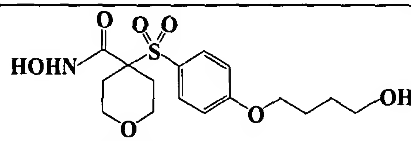
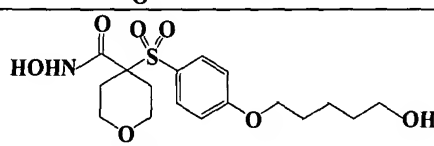
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
417		463.1539	463.1546		315		2.6	
418				>10000	1500	>10000	64	>10000
419					120		4	
420				>10000	67	>10000	4	>10000
421					649		256	

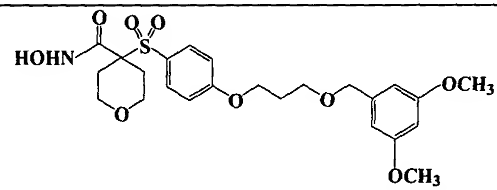
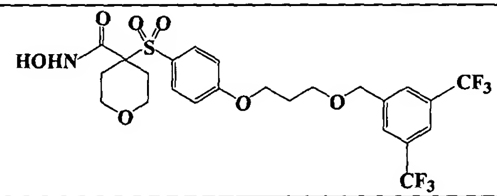
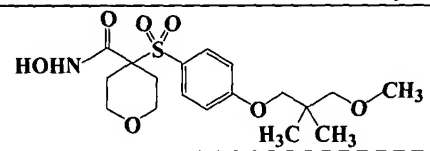
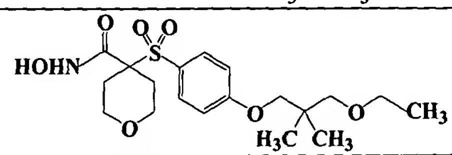
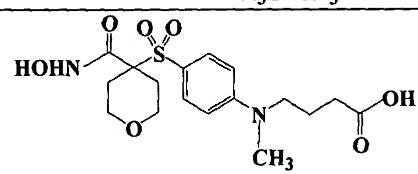
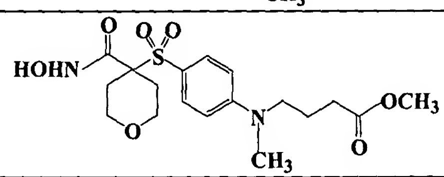
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
422					7200		1484	
423					9000		1585	
424					485		192	
425					>10000		3308	
426					>10000		5151	
427					251		114	

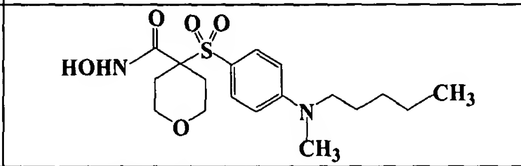
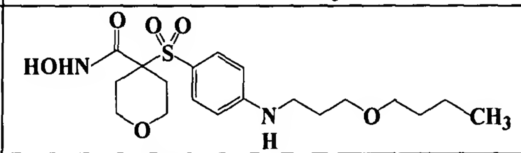
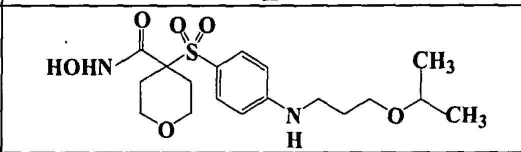
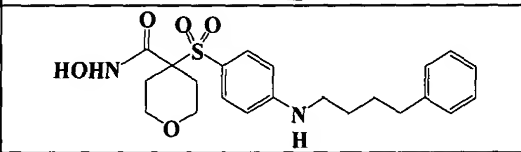
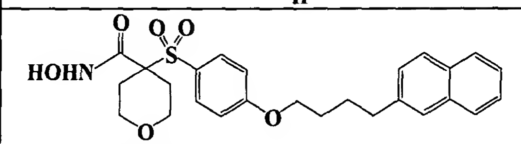
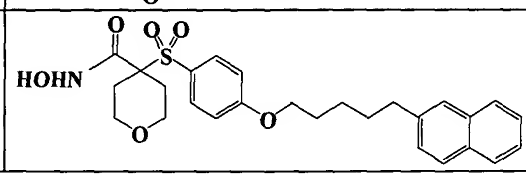
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
428					20		1.4	
429					6.5	>10000	0.5	>10000
430					2700		195	
431					115		4	
432					7		1.5	
433					220		7	

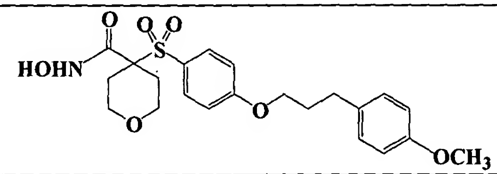
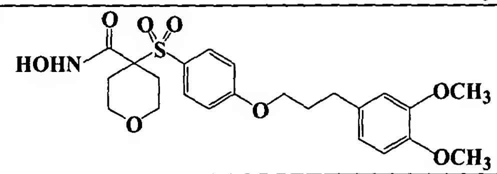
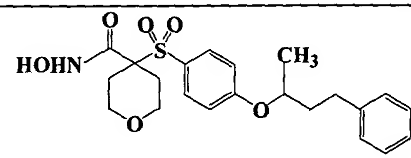
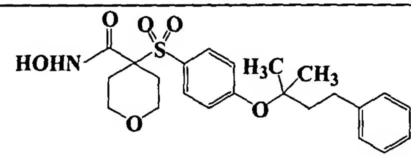
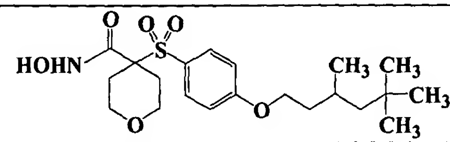
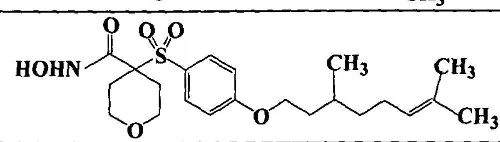
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
434					1.1		0.6	
435				>10000	>10000		500	
436				>10000	1500		100	
437				>10000	>10000	>10000	90	>10000
438				>10000	505	3800	11	>10000
439				>10000	2000	6000	25	>10000

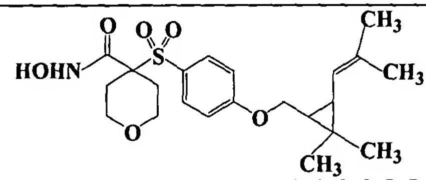
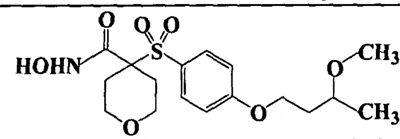
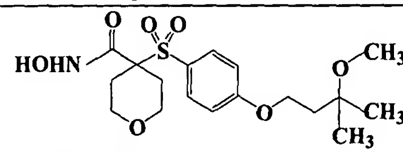
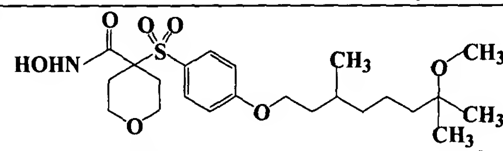
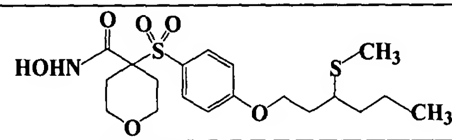
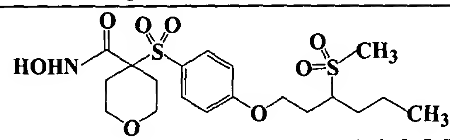
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
440				>10000	4	140	1	2500
441				9000	13	110	2	2290
442				>10000	6.2	5.4	1.8	997
443				>10000	25	375	3.5	2429
444					8.9		7.6	
445				3325	2.2	44	0.5	546

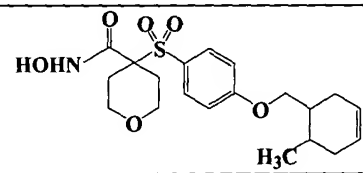
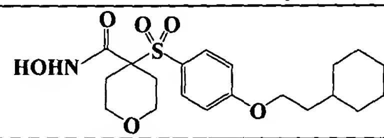
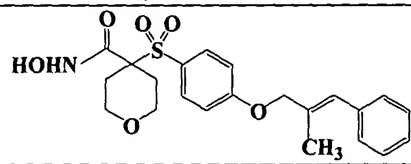
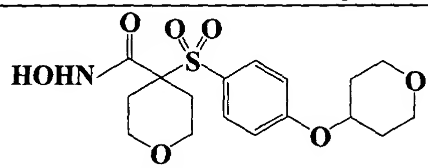
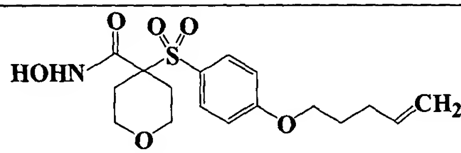
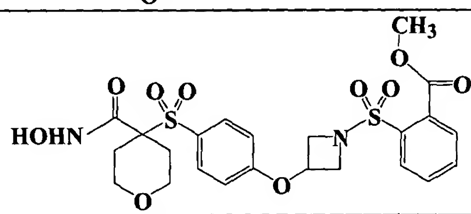
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
446					76		6.6	
447				>10000	8.9	12.2	2	1360
448				3080	9	116	2.7	832
449				1929	3.7	41	7	58
450				>10000	6.6	44	0.9	4937
451					4.7		9	
452					2.2		14.8	

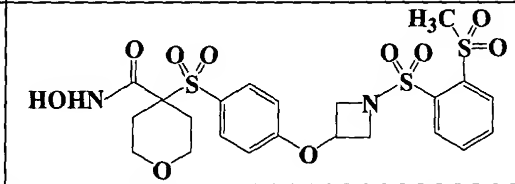
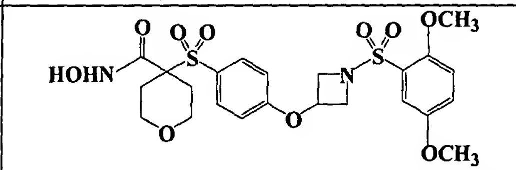
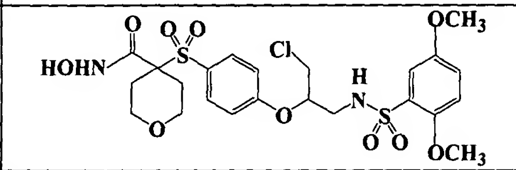
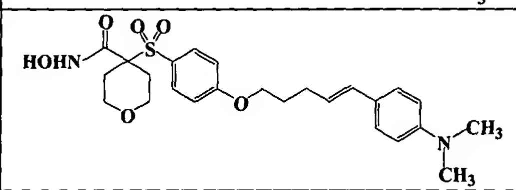
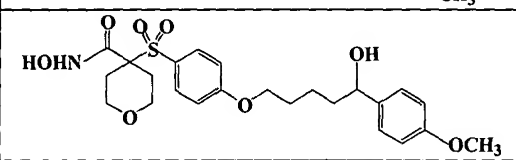
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
453				>10000	13	800	3	5000
454				>10000	165		27	
455					900		690	
456					425		350	
457				>10000	>10000		>10000	
458				>10000	3500		1400	

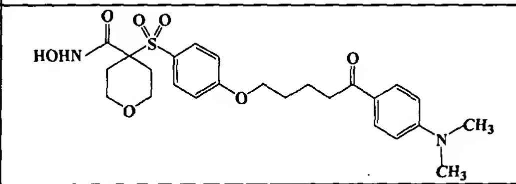
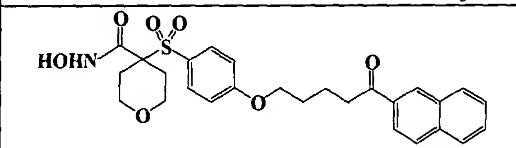
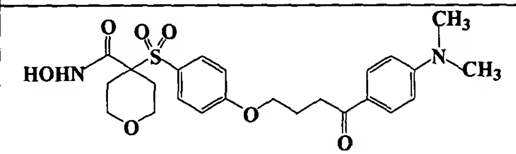
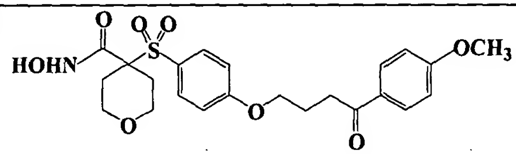
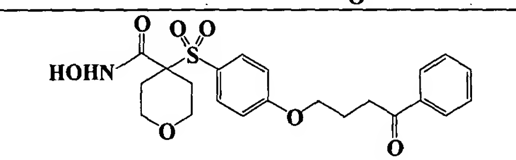
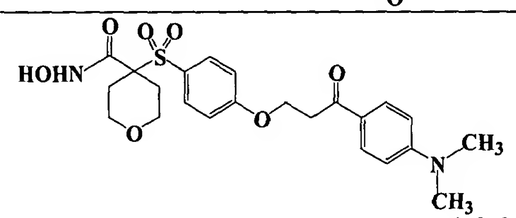
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
459				>10000	700		670	
460				>10000	145	700	25	>10000
461				>10000	2200		590	
462				>10000	11	18	7	6500
463		484.1794	484.1776		17		7	
464		498.195	498.1925		46		1.4	

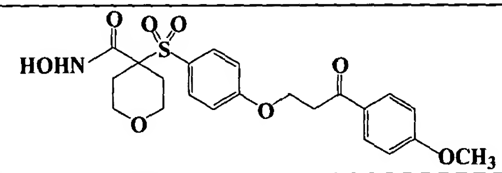
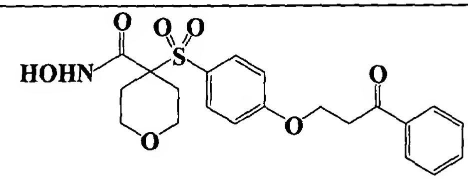
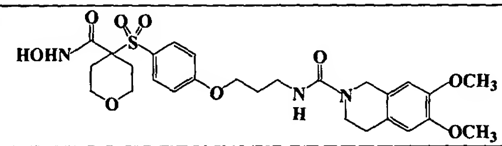
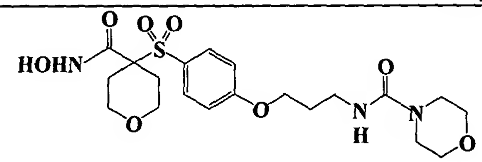
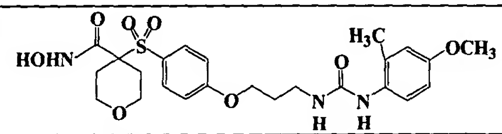
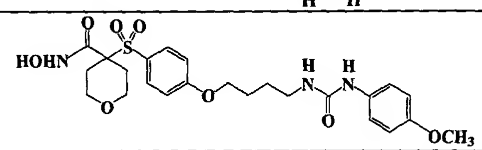
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
465		450.1586	450.1577	>10000	4	180	0.3	1800
466		480.1692	480.1732	>10000	110	45	15	>10000
467				>10000	940	450	120	>10000
468				>10000	2500		1500	
469				>10000	145		60	
470				>10000	7		3	

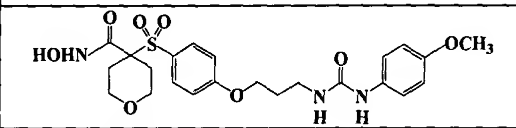
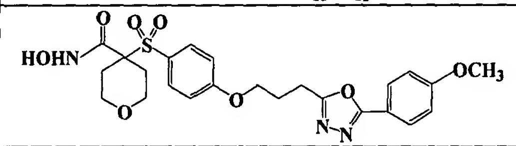
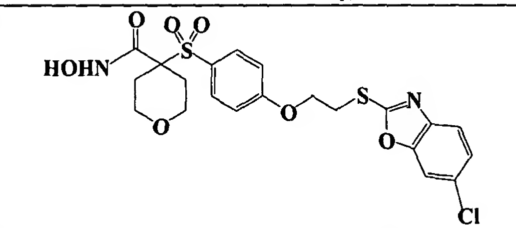
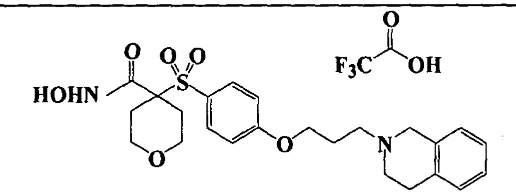
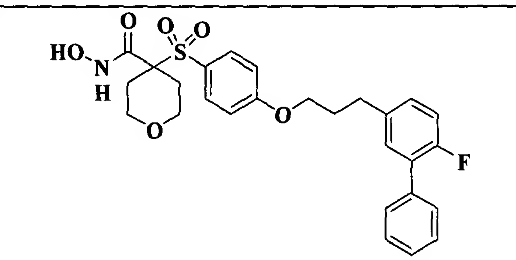
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
471				>10000	270		120	
472				>10000	3	40	6	400
473				>10000	5	45	5	600
474				>10000	12		3	
475				>10000	30	120	2	3600
476				>10000	2500	>10000	230	>10000

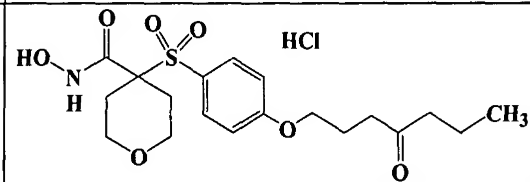
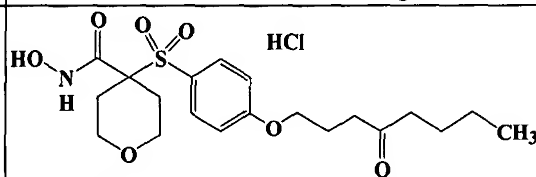
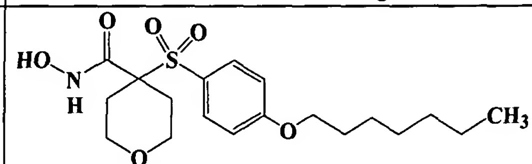
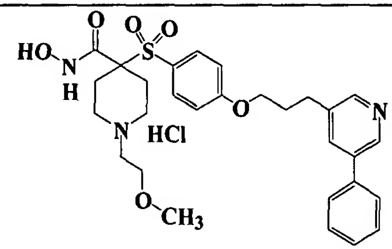
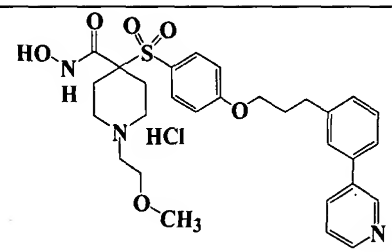
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
477				1300	1.5		2	
478				>10000	1	34	5	1450
479				2700	4	14	3	2000
480				4200	18	60	11	1400
481					1.3		2	
482					3300		40	

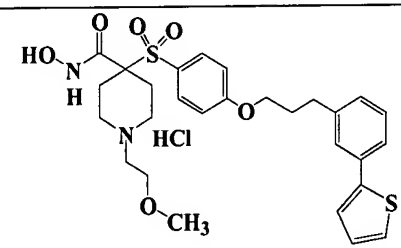
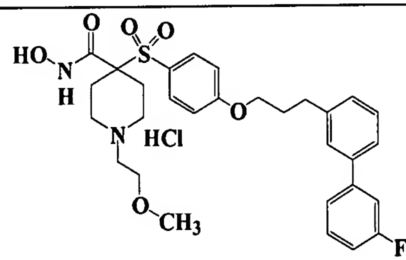
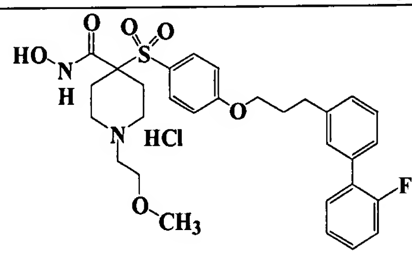
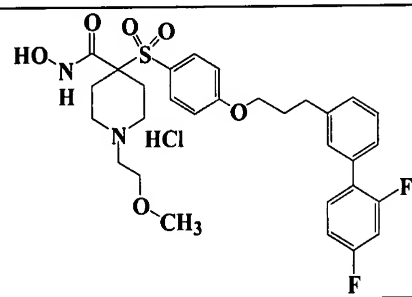
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
483					2000		29	
484					640		12	
485					4000		64	
486				>10000	106	255	4.6	>10000
487				>10000	3.1	169	0.5	1570

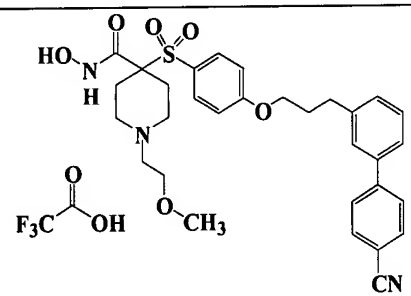
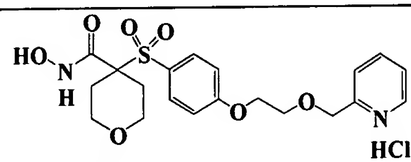
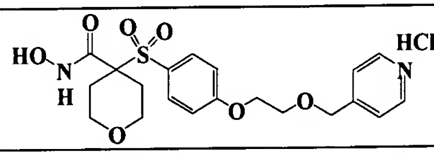
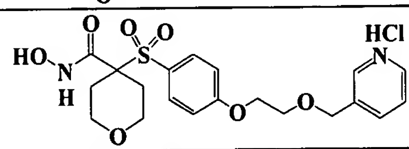
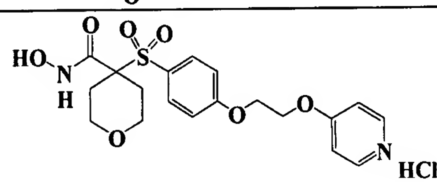
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
488		505.2008	505.1991					
489		512.1743	512.1766	>10000	58.2	>10000	0.4	>10000
490		491.1852	491.1856	>10000	18.2	928	0.2	5630
491		478.1536	478.1540	7310	6.8	94.2	0.8	981
492		448.1430	448.1428	3550	3.5	67.3	0.7	574
493		471.1695	471.1695	4770	15.9	752	0.9	3230

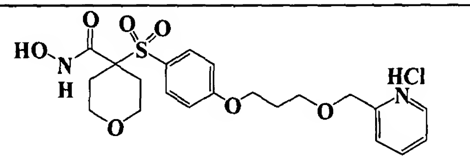
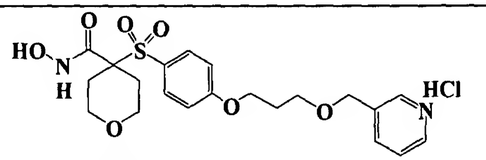
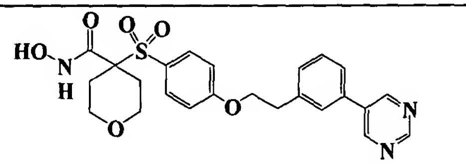
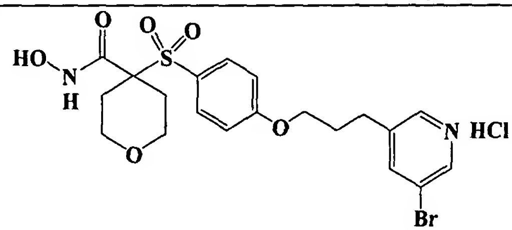
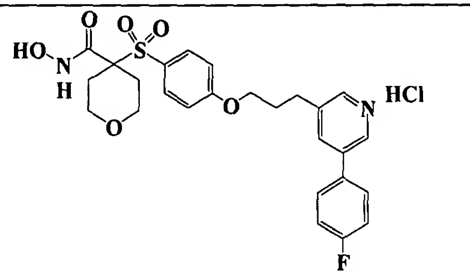
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
494		464.1392	464.1379	1520	<0.1	13.6	<0.1	197
495		434.1273	434.1277	815	1.9	25.8	1.7	505
496		578.2172	578.2164		242		8.4	
497		472.1754	472.1769		1450		23.5	
498		522.191	522.1915		160		14.8	
499		508.1754	508.1753		56.2		7.0	

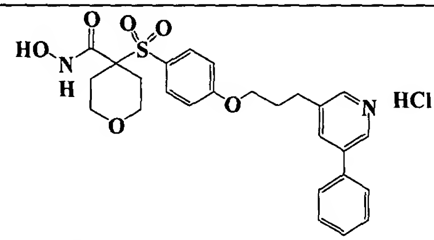
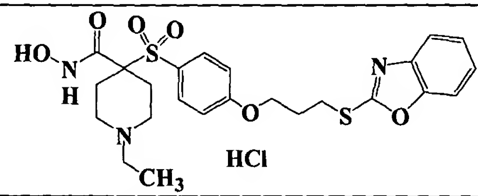
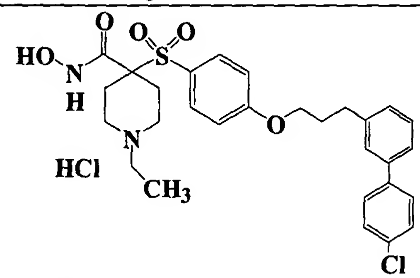
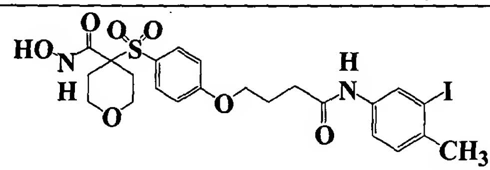
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
500		494.1597	494.1596	2390	1,9	63.2	8.5	2960
501		518.1597	518.158	>10000	184	7710	1.4	>10000
502		513.0557	513.0574	>10000	22.7	160	1.0	5640
503		475.1903	475.1907					
504		514.1700	514.1735	(>10000)	(434)	(2310)	(4.65)	(>10000)

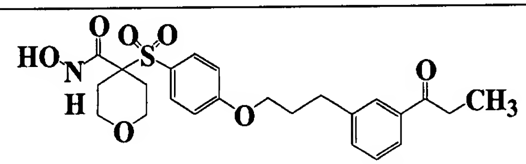
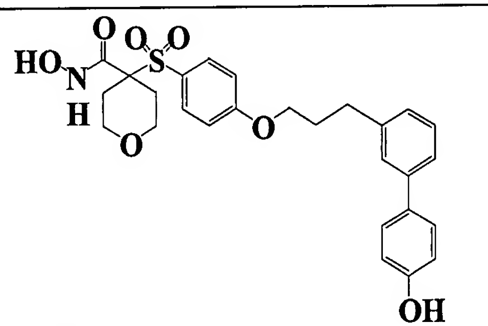
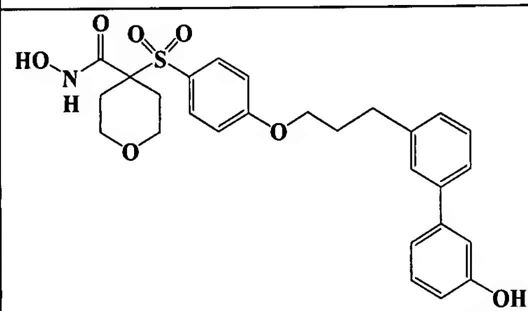
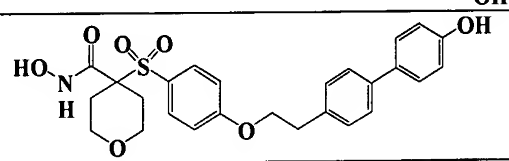
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
505		414.1581	414.1586	(850)	(2.56)	(10.2)	(0.81)	(962)
506		428.1738	428.1751	(1465)	(1.92)	(11.4)	(0.23)	(681)
507		400.1767	400.1788	(3590)	(0.84)	(0.44)	(0.19)	(444)
508		554.2319	554.2347	(4850)	(22.8)	(160)	(0.141)	(2790)
509		554.2319	554.2308	(>10000)	(89.26)	(50.85)	(0.297)	(4158.92)

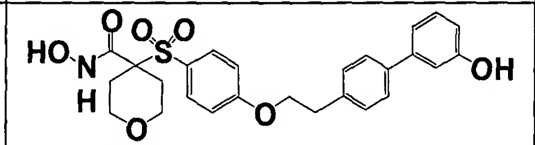
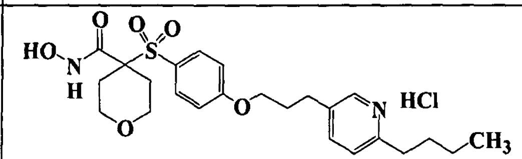
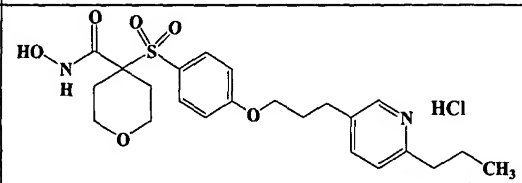
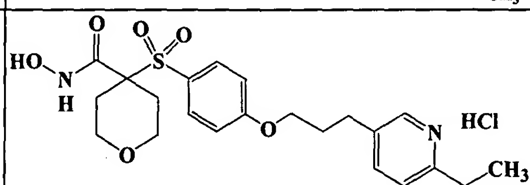
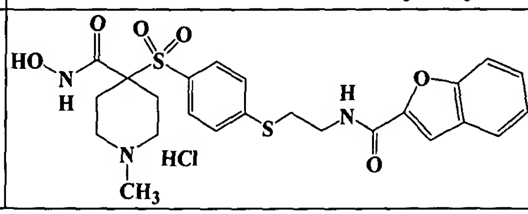
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
510				(>10000)	(7.85)	(39.82)	(0.25)	(2183.66)
511		571.2273	571.2255	(>10000)	(525.78)	(38.53)	(1.36)	(>10000)
512		571.2273	571.2281	(>10000)	(757.99)	(25.71)	(1.07)	(>10000)
513		589.2178	589.2193	(>10000)	(879.71)	(254.58)	(0.98)	(9274.4)

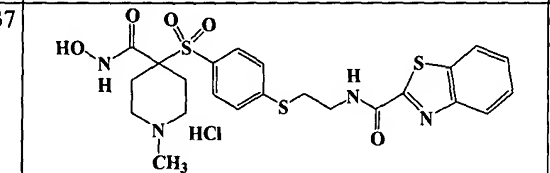
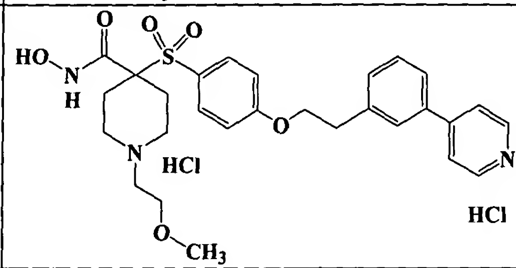
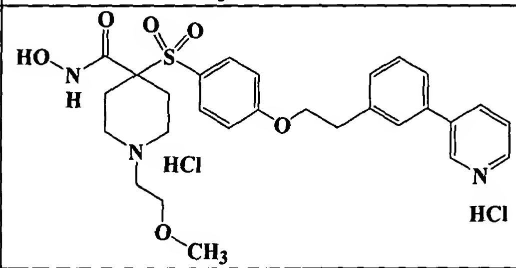
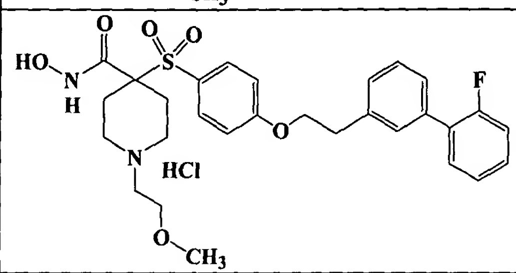
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
514		578.2319	578.2305	(>10000)	(292.63)	(223.53)	(0.28)	(4082.05)
515				>10000	89.76	154.32	24.23	>10000
516				>10000	41.94	119.72	9.55	9434.24
517				>10000	34.66	137.63	6.19	>10000
518				>10000	26.35	115.39	169.48	967.13

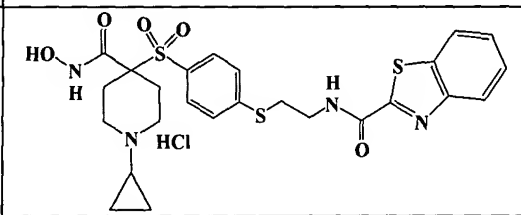
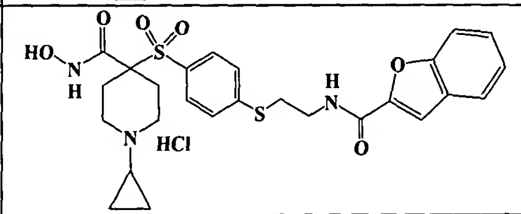
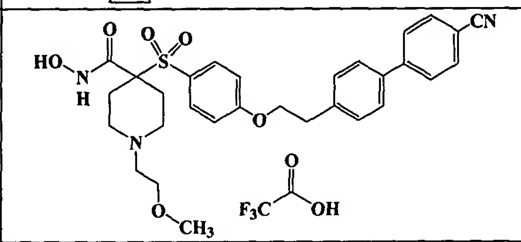
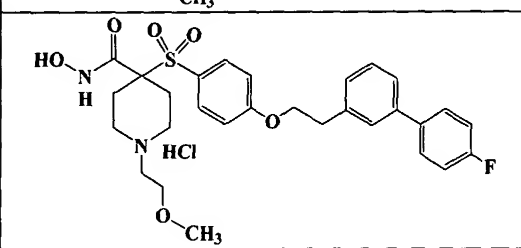
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
519				>10000	170.25	421.64	2.18	>10000
520				>10000	54.24	36.38	0.62	4296.13
521					62.0		5.8	
522				(>10000)	12.9 (32.1)	(135)	0.3	(6290)
523		515.1647	515.1690	8069 (3213)	161.6 (196.7)	1647.2 (1253)	0.3 (0.234)	>10000 (>10000)

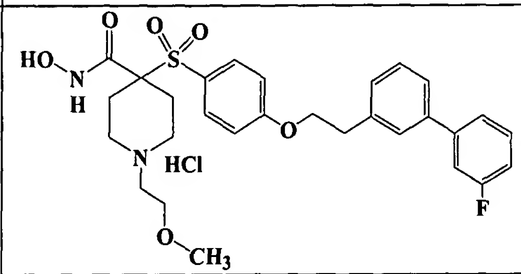
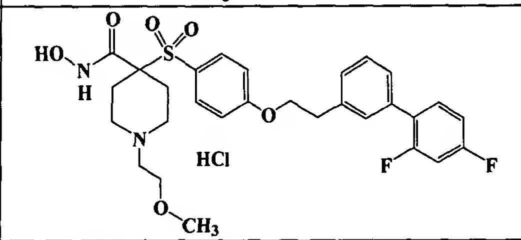
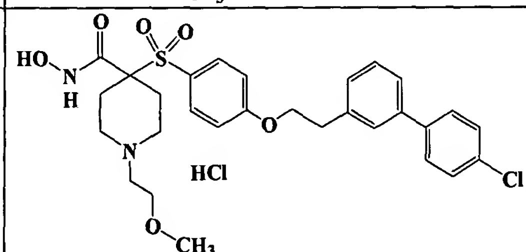
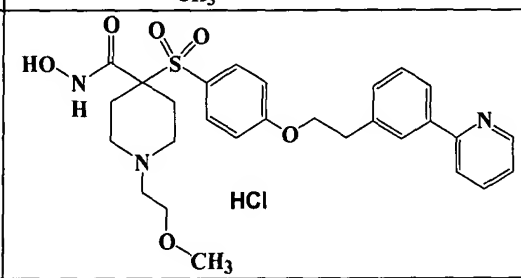
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
524		497.1741	497.1763	>10000	38.3 (51.8)	1841.5 (739.5)	0.2 (0.244)	>10000 (>10000)
525		520.1576	520.1581		7.5		1.5	
526		557.1871	557.1863 557.1843	(>10000)	(1680)	(2070)	(3.96)	(>10000)
527				(5100)	(21.3)	(30.4)	(.044)	(1360)

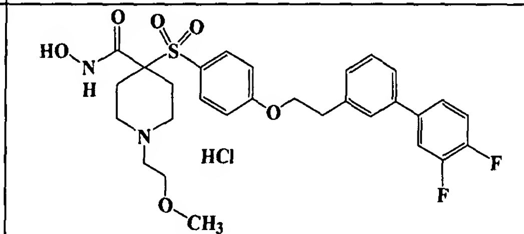
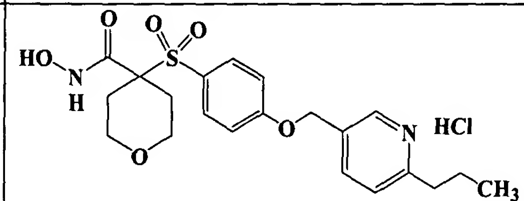
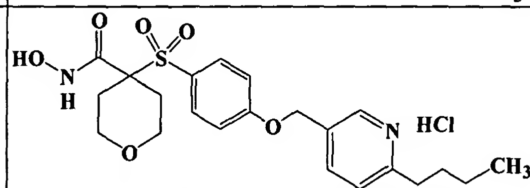
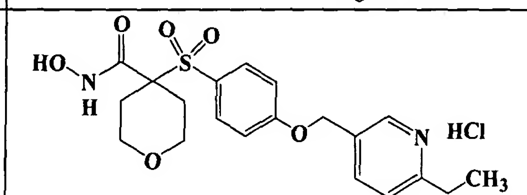
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
528				(>10000)	(83.5)	(238)	(2.57)	(5700)
529		529.2003	529.1982	(>10000)	(3550)	(1870)	(20.2)	(>10000)
530		512.1738	512.1774	(>10000)	(699)	(220)	(7.33)	(>10000)
531		498.1581	498.1614	(>10000)	(337)	(774)	(2.72)	(>10000)

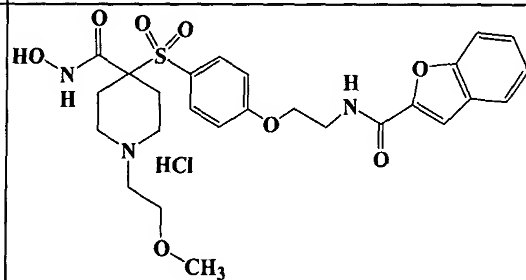
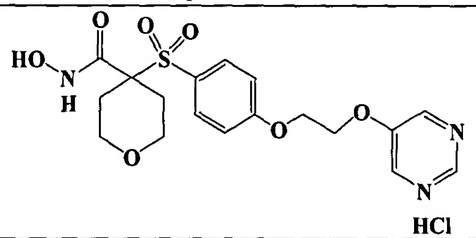
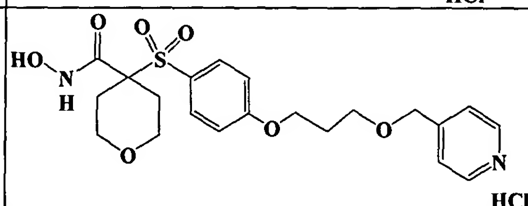
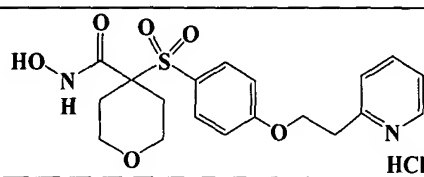
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
532		498.1581	498.1610	(>10000)	(739)	(1320)	(1.02)	(>10000)
533				(>10000)	(29.3)	(141)	(0.226)	(6680)
534				(>10000)	(25.4)	(324)	(0.493)	(6810)
535				(>10000)	(23.2)	(128)	(0.261)	(3870)
536				(>10000)	(744)	(3400)	(3.4)	(>10000)

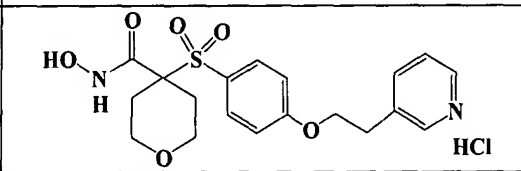
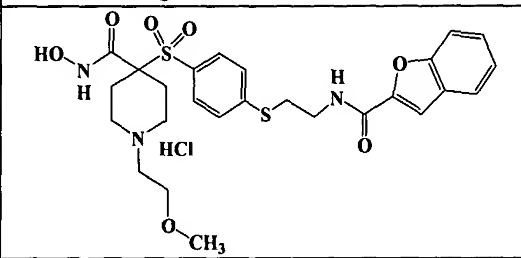
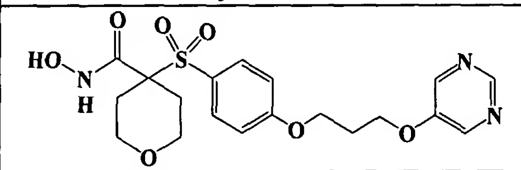
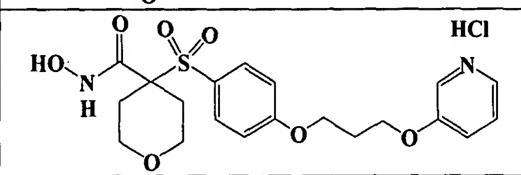
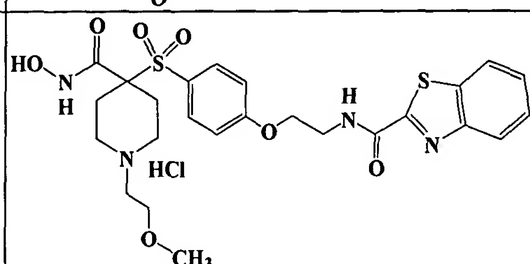
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
537		535.1138	535.1160	(>10000)	(985)	(900)	(0.657)	(>10000)
538		540.2163	540.2142	(>10000)	(24.6)	(117)	(0.184)	(1700)
539		540.2163	540.2160	(9130)	(38.6)	(85.5)	(0.21)	(1180)
540		557.2116	557.2132	(>10000)	(270)	(689)	(0.58)	(>10000)

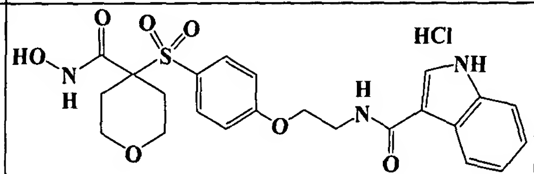
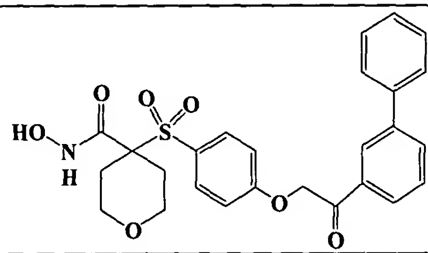
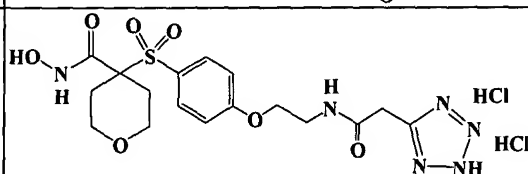
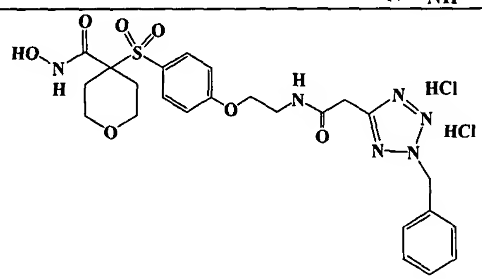
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
541		561.1295	561.1266	(>10000)	(302.15)	(269.03)	(0.24)	(>10000)
542		544.1571	544.1566	(>10000)	(234.13)	(921.73)	(0.86)	(>10000)
543		564.2163	564.2192	(>10000)	(124.15)	(207.41)	(0.23)	(3094.73)
544		557.2116	557.2087	(>10000)	(302.23)	(787.01)	(0.898)	(>10000)

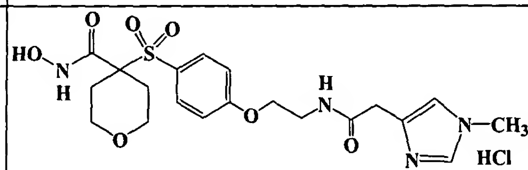
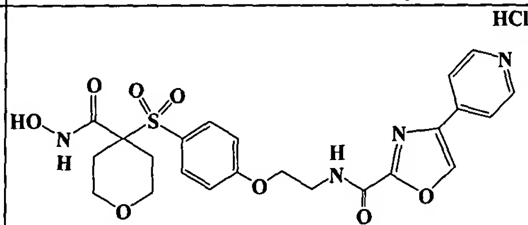
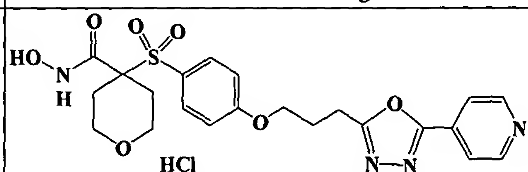
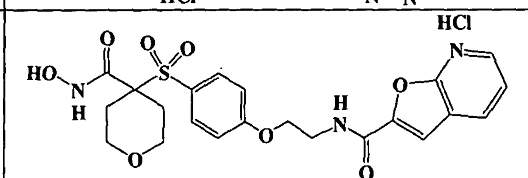
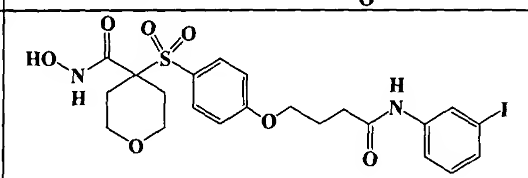
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
545		557.2116	557.2101	(>10000)	(309.81)	(922.55)	(1.11)	(>10000)
546		575.2022	557.5023	(>10000)	(426.17)	(1269.5)	(1.06)	(>10000)
547		573.1821	573.1848	(>10000)	(727.08)	(1863.44)	(2.28)	(>10000)
548		540.2163	540.2193	(>10000)	(1.58)	(278.57)	(0.38)	(7415.08)

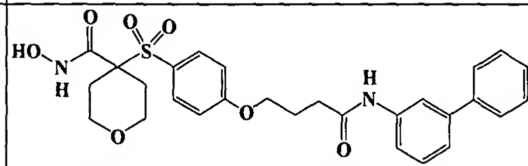
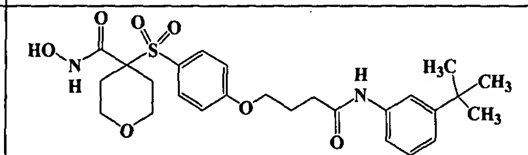
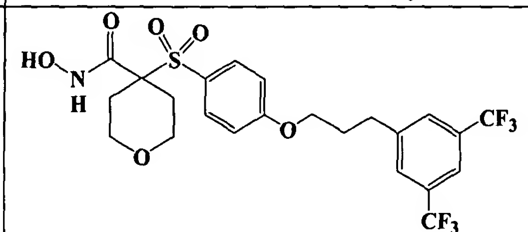
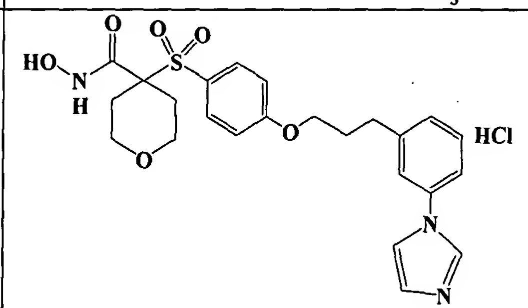
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
549		575.2022	575.2042	(>10000)	(503.95)	(1770.79)	(1.87)	(>10000)
550				(>10000)	(5.49)	(7.51)	(0.52)	(2180)
551				(>10000)	(5.07)	(48.2)	(0.62)	(2055)
552				(>10000)	(4.94)	(2.22)	(1.78)	(2440)

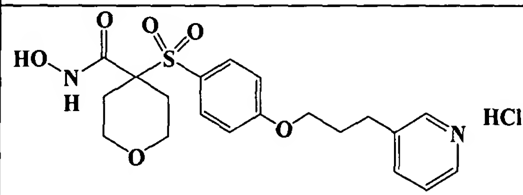
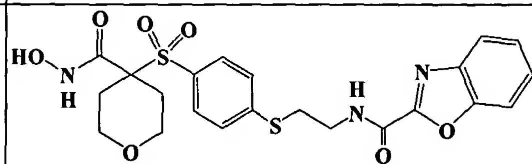
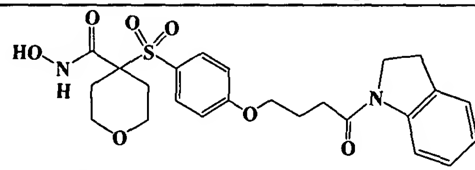
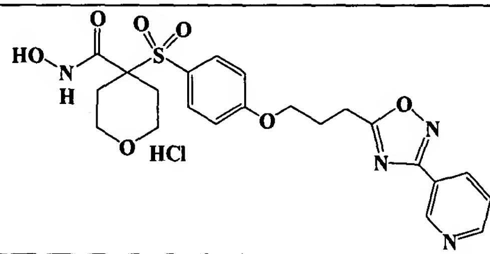
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
553		546.1905	546.1896	(>10000)	(7.797)	(71.205)	(0.259)	(2257.112)
554				(>10000)	(61.27)	(442.07)	(14.50)	(>10000)
555				(>10000)	(3.383)	(50.012)	(0.261)	(688.63)
556				(8972.84)	(68.058)	(211.92)	(53.22)	(3496.68)

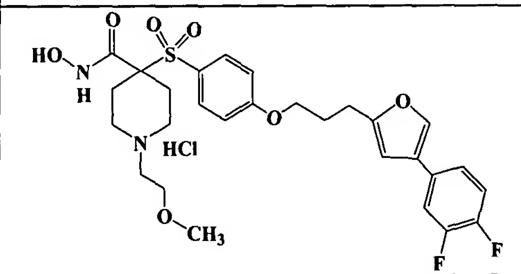
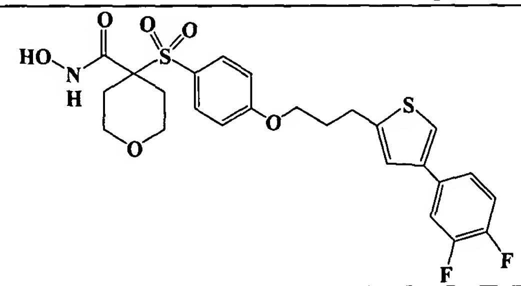
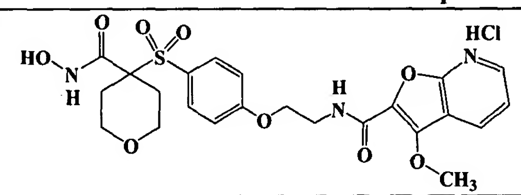
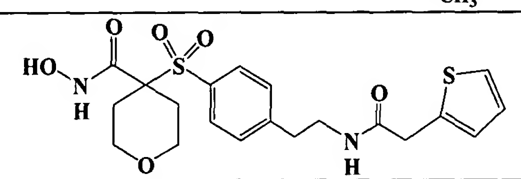
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
557				(>10000)	(6.46)	(33.57)	(3.68)	(52.23)
558		562.1676	562.1714	(>10000)	(352.06)	(1357.7)	(2.163)	(>10000)
559				(>10000)	(11.65)	(57.56)	(1.51)	(845.5)
560				(>10000)	(10.26)	(7.17)	(0.616)	(549.16)
561		579.1400	579.1389	(>10000)	(336.04)	(467.44)	(0.31)	(>10000)

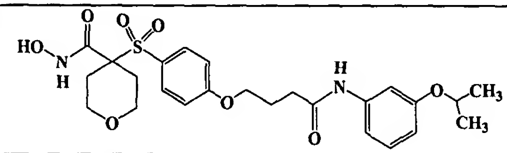
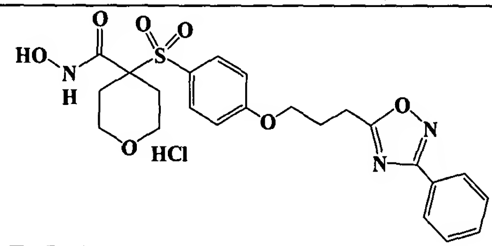
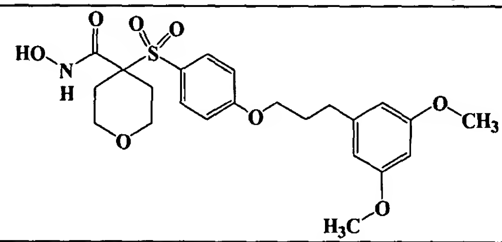
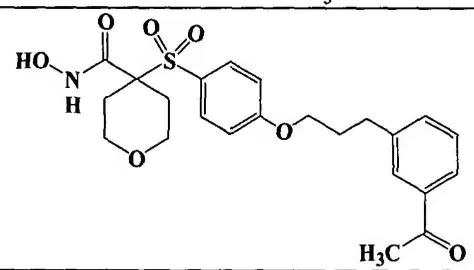
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
562		488.1486	488.1476	(2738.33)	(241.03)	(785.83)	(2.97)	(9265.67)
563		496.1425	496.1453	(>10000)	73.5 (70.11)	(132.06)	1.1 (0.70)	(4400.5)
564		455.1343	455.1345		144.9		19.4	
565		545.1813	545.1825		14.0		1.6	

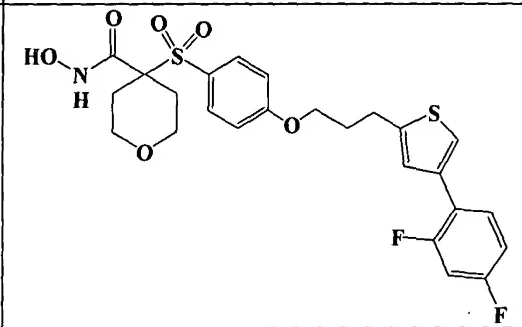
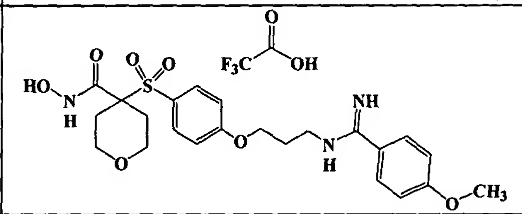
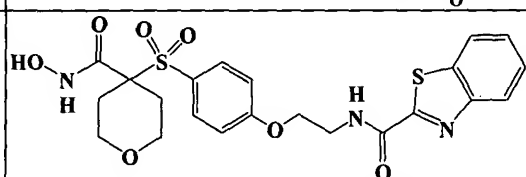
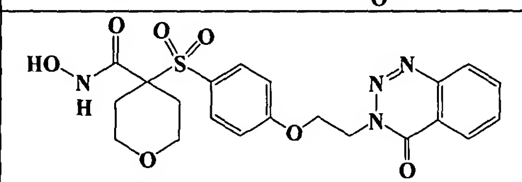
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
566		467.1595	467.1643		65.7		18.8	
567		549.0931	549.0955		660.5		21.9	
568		489.1438	489.1435		21.0		1.5	
569		506.1050	506.1028		1405		171.8	
570				(3061.49)	4.8 (10.09)	(6.15)	0.2 (0.142)	(1357.46)

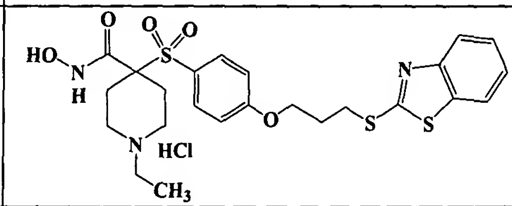
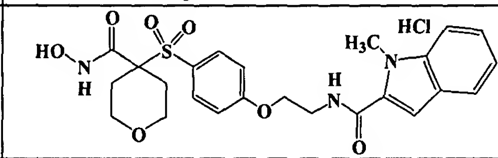
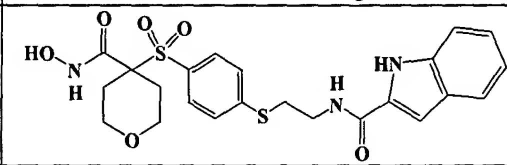
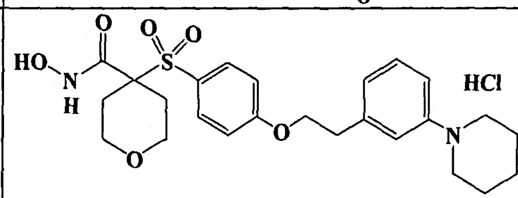
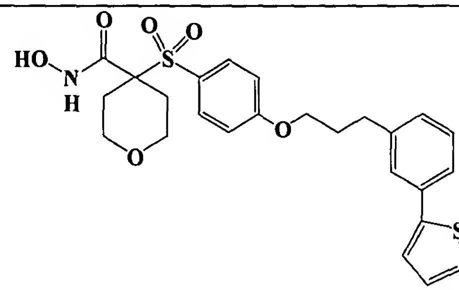
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
571					11.9		1.6	
572					37.3		4.7	
573		556.1223	556.1214		1707.7		75.1	
574				(>10000)	29.4 (112.25)	(83.02)	0.7 (1.32)	(5386.06)

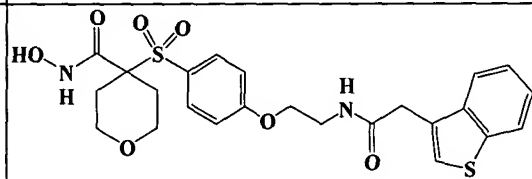
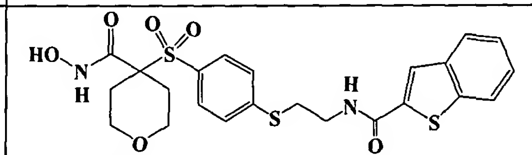
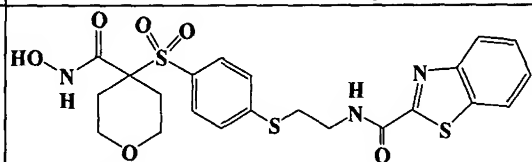
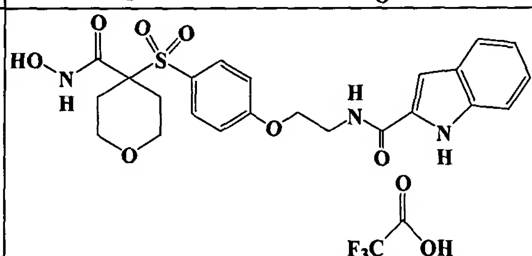
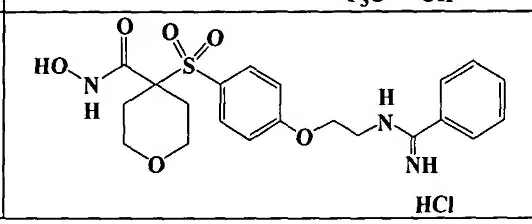
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
575					8.4		2.0	
576		506.1050	506.1069	>10000	232.7	397.0	0.3	>10000
577					48.2		1.2	
578		489.1438	489.1428	(>10000)	20.5 (72.1)	(578)	2.9 (1.72)	(>10000)

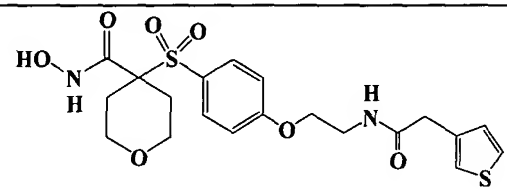
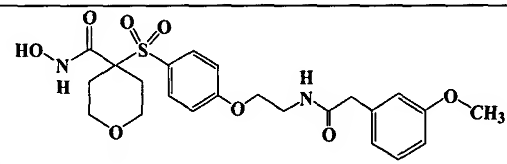
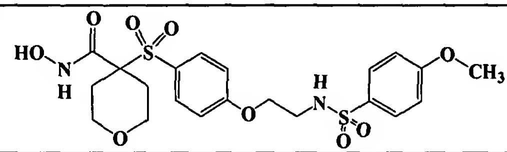
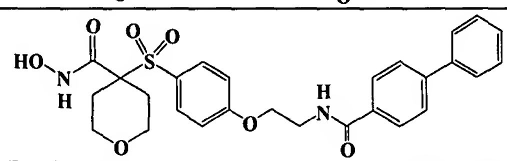
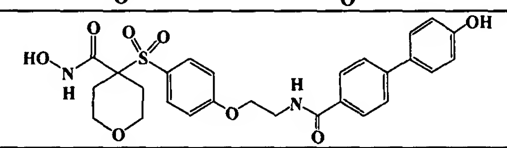
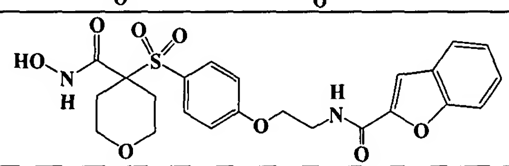
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
579		595.1743	595.1767	>10000	37.8	136.0	0.4	>10000
580		555.1430	555.1454	>10000	136.0	417.2	0.6	>10000
581		536.1156	536.1173		2534.3		29.8	
582		460.1571	460.1573		55.7		25.3	

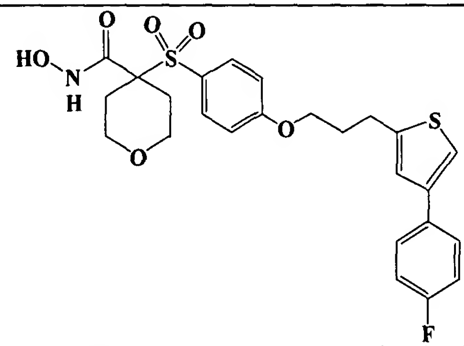
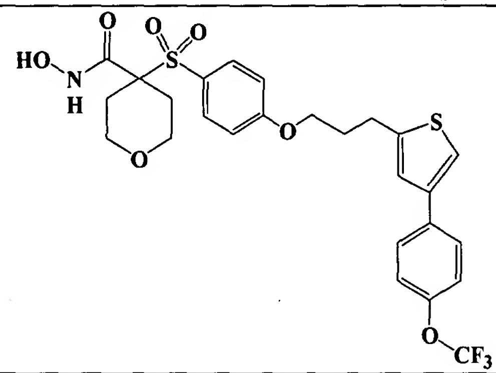
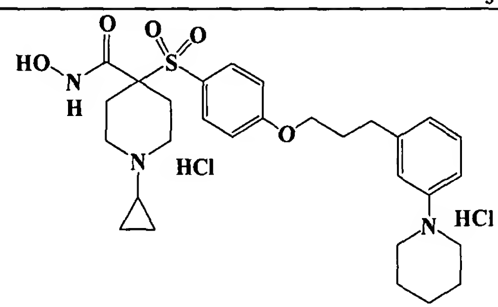
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
583					15.7		1.6	
584				(2760)	72.9 (20.8)	(12.6)	3.6 (0.944)	(6630)
585					85.4		4.0	
586					10.1		0.6	

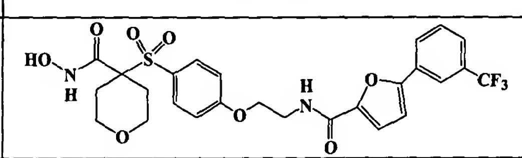
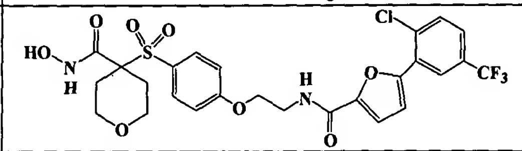
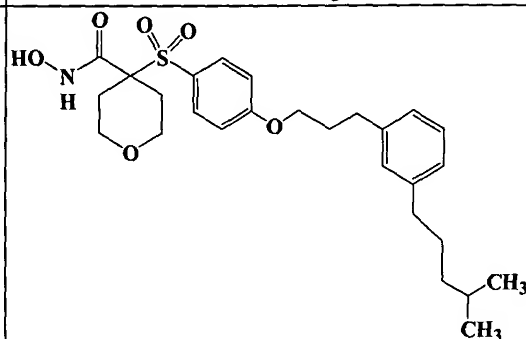
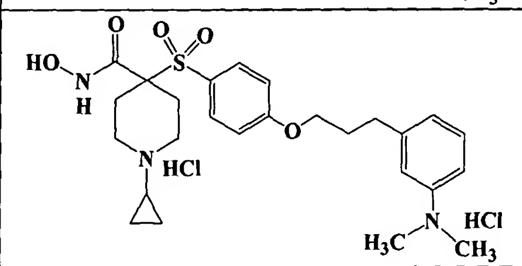
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
587		538.1164	538.1191	>10000 (>10000)	81.7 (124.9)	1372.9 (8180)	0.1 (1.424)	>10000 (4154)
588		492.1804	492.1773		94.9		15.0	
589		506.1050	506.1054		9.9		0.4	
590					857.7		48.0	

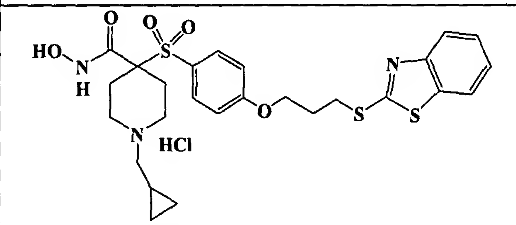
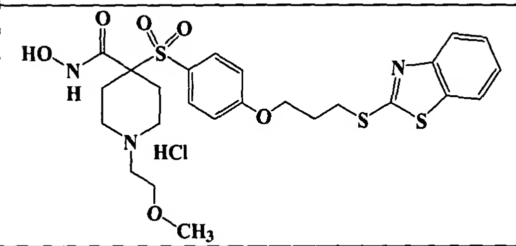
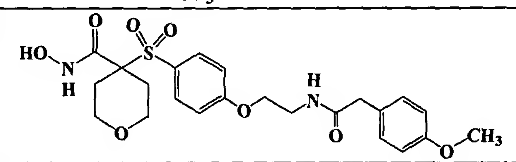
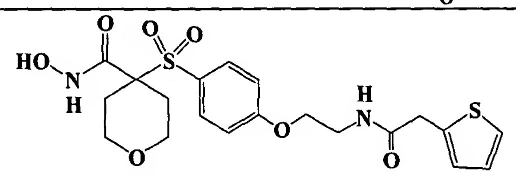
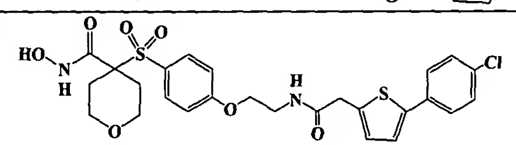
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
591		536.1348	536.1372	>10000 (>10000)	3.5 (4.4)	12.0 (4.22)	0.3 (0.19)	>10000 (8742.7)
592		502.1648	502.1639		336.4		38.7	
593		504.1263	504.1254		6.5		15.6	
594					140.1		3.8	
595		502.1353	502.1359	>10000 (>10000)	482.5 (586.2)	1733 (2056.6)	1.0 (7.245)	>10000 (>10000)

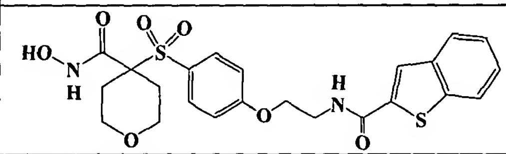
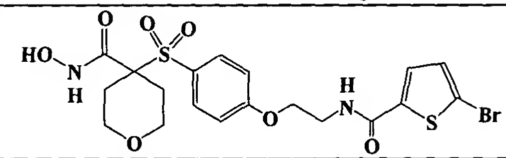
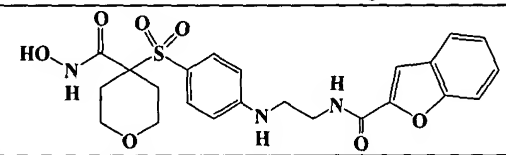
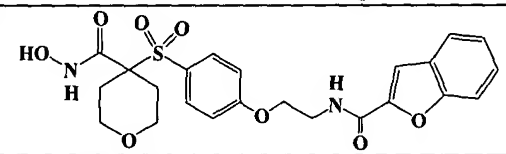
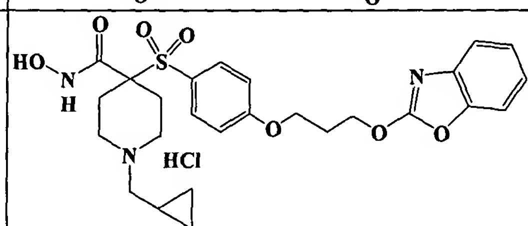
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
596		519.1260	519.1265	>10000 (>10000)	10.3 (11.2)	194.5 (307.7)	2.7 (0.398)	2491 (1160)
597		521.0875	521.0910		471.1		12.1	
598		522.0827	522.0932	(>10000)	(599.35)	(705.33)	(0.27)	(>10000)
599		488.1491	488.1491	>10000 (>10000)	<0.1 (0.38)	11.6 (11.34)	0.1 (0.24)	57.01
600		448.1542	448.1542		205.7		214.4	

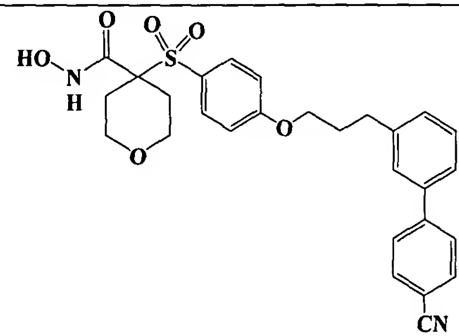
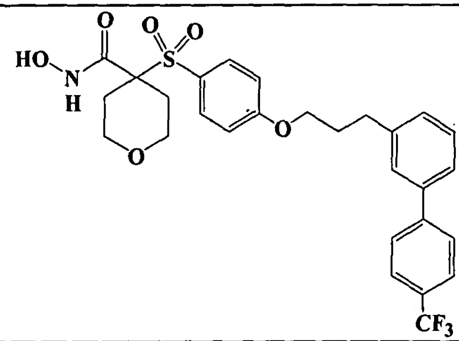
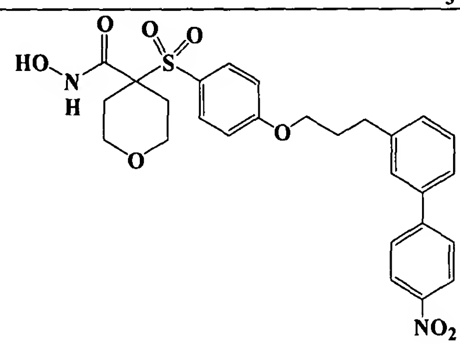
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
601		469.1103	469.1093	4916	1.9	42.6	1.3	2062
602		493.1639	493.1608		13.7		3.6	
603		515.1158	515.1145		34.0		2.4	
604					36.6		3.3	
605					44.0		3.8	
606		489.1332	489.1326	>10000 (>10000)	5.0 (11.574)	234.0 (105.89)	0.4 (0.432)	2566 (2053.20)

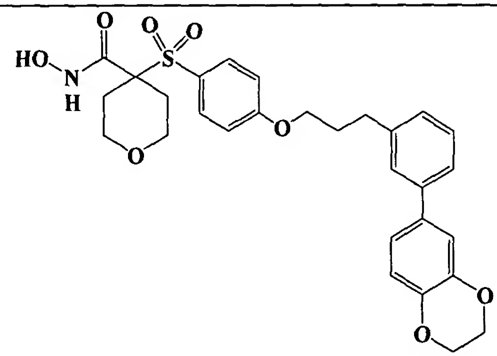
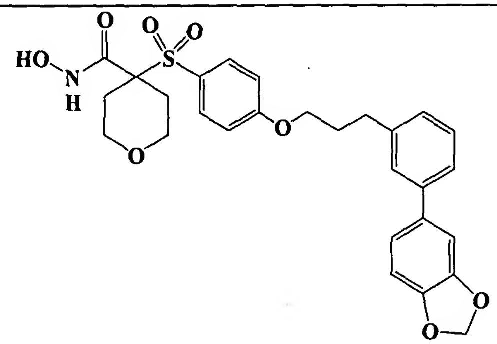
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
607		520.1264	520.1297	>10000	45.2	2298	0.1	>10000
608		586.1181	586.1160	>10000 (>10000)	342.1 (723.95)	1794 (1368.3)	6.6 (9.34)	>10000 (>10000)
609				>10000	579.9	6887	7.7	>10000

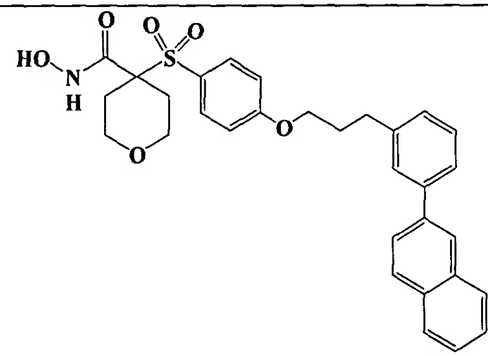
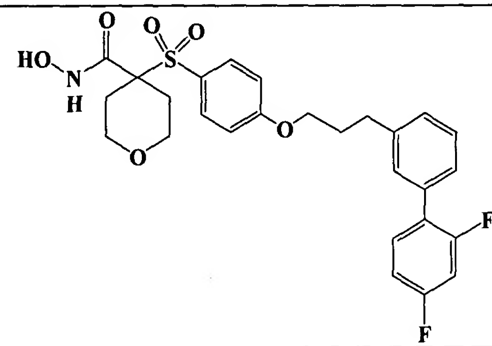
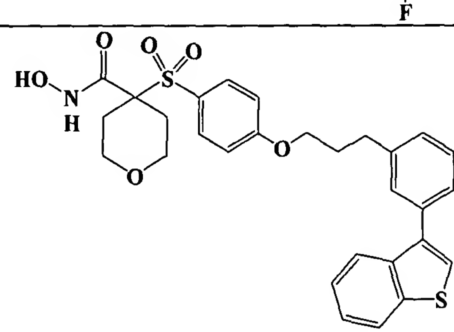
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
610					488.3		4.1	
611					733.2		13.6	
612		504.2414	504.2413		1232.2		16.1	
613					34.3		6.6	

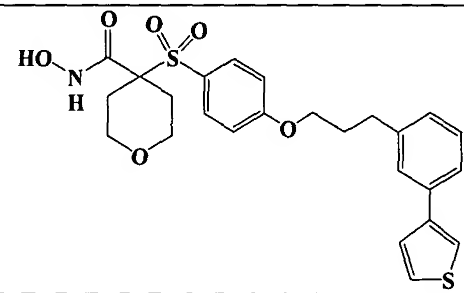
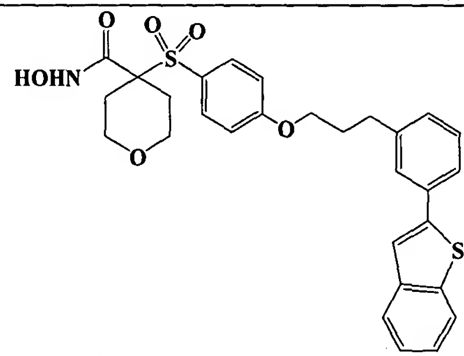
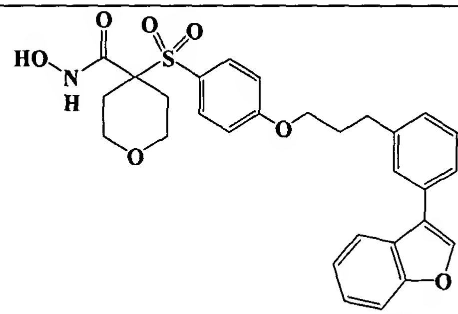
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
614		562.1504	562.1516	>10000	1.8	8.5	0.7	9440
615		566.1443	566.1453	>10000	1.1	3.6	0.4	6696
616		493.1645	493.1617	1584	5.3	54.8	2.0	1969
617		469.1103	469.1086	2074 1112	0.8	413	0.6	4133
618					822.1		27.5	

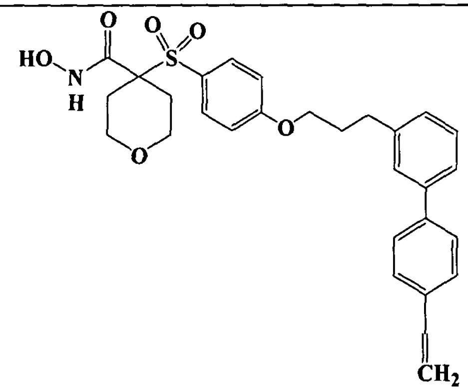
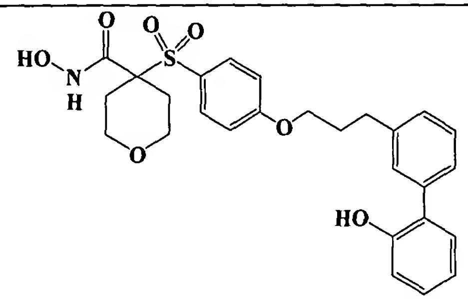
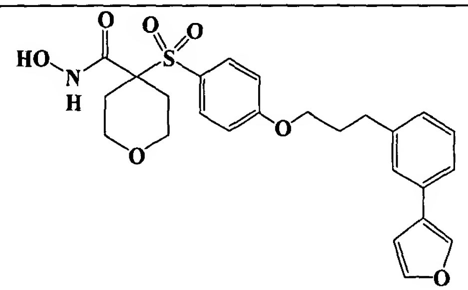
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
619					66.2		1.5	
620					16.2		4.1	
621		488.1491	488.1489		367.6		17.8	
622		505.1103	505.1120	>10000 (>10000)	273.1 (450.85)	1756 (2077.1)	1.5 (2.68)	>10000 (>10000)
623		546.1733	546.1728	>10000	5.2	3.1	1.2	5520

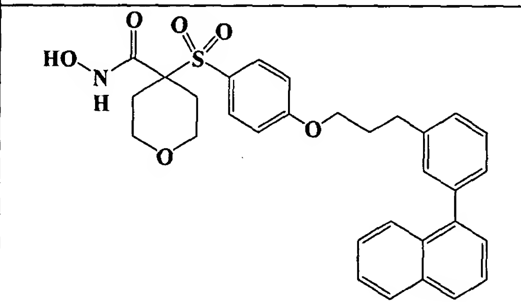
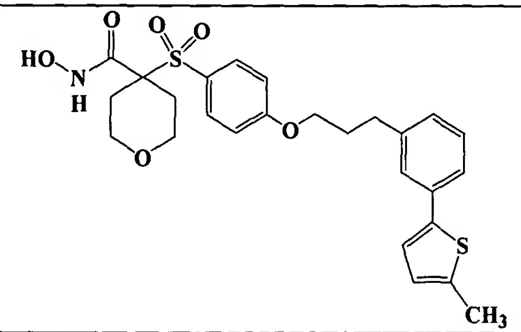
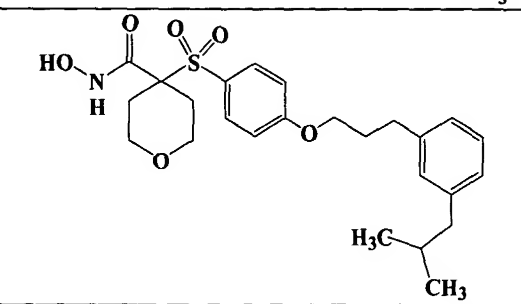
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
624		521.1746	521.1753	>10000 (>10000)	214.4 (623)	1029 (443)	0.3 (0.9)	>10000 (7580)
625		564.1668	564.1643	(>10000)	3499.5 (6860)	(4600)	33.6 (43.6)	(>10000)
626		558.191	558.1925	>10000 (>10000)	142.8 (645)	885 (1100)	0.4 (7.5)	>10000 (>10000)

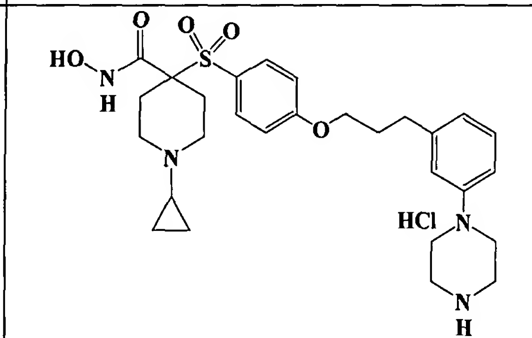
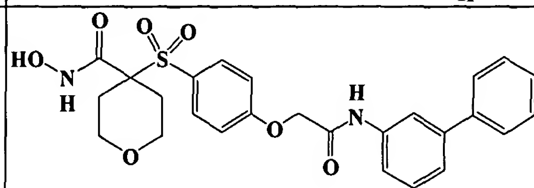
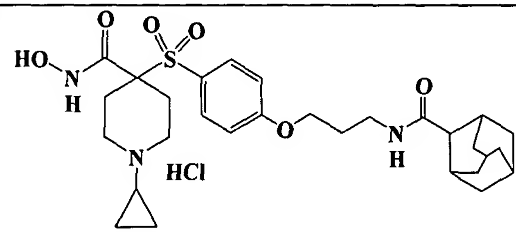
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
627		554.1849	554.1884	(>10000)	2072.7 (3950)	(3150)	14.9 (40.9)	(>10000)
628		540.1692	540.1712	>10000 (>10000)	1701.3 (2750)	1754 (1930)	3.3 (19.8)	>10000 (>10000)

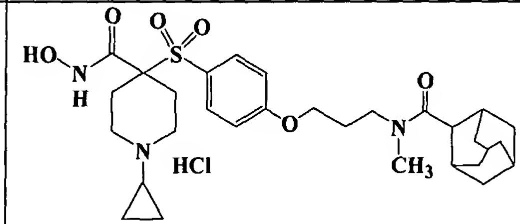
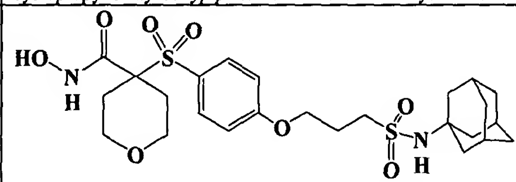
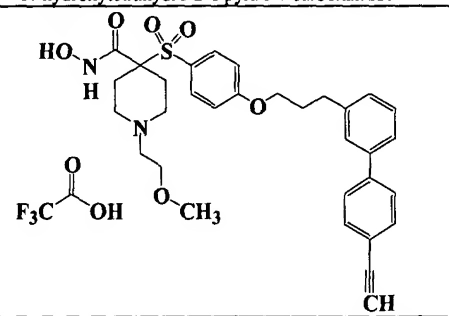
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
629		546.1950	546.1965	(>10000)	536.8 (1020)	(1300)	78.6 (89.1)	(>10000)
630		532.1605	532.1598	>10000 (>10000)	1166.6 (2070)	5990 (2280)	0.4 (6.02)	>10000 (>10000)
631		552.1515	552.1520	(>10000)	2143.2 (4960)	(5810)	117.7 (57.6)	(>10000)

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
632		502.1358	502.1387	>10000 (>10000)	91.0 (279)	411 (716)	1.6 (6.54)	>10000 (>10000)
633		552.1515	552.1510	(>10000)	2828.1 (4580)	(6780)	117.0 (92.4)	(>10000)
634		536.1743	536.1730	(>10000)	486.4 (983)	(1300)	16.3 (19.4)	(>10000)

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
635		522.1950	522.1973	(>10000)	2309.5 (4680)	(4830)	20.0 (26.2)	(>10000)
636		512.1743	512.1755	(>10000)	195.0 (527)	(763)	3.2 (3.21)	(>10000)
637		486.1586	486.1576	>10000 (>10000)	137.6 (498)	830 (881)	1.8 (4.63)	>10000 (>10000)

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
638		546.1950	546.1950	(>10000)	4400.9 (8120)	(8770)	400.4 (68.1)	(>10000)
639		516.1515	516.1501	(>10000)	247.1 (505)	(688)	4.3 (12.5)	(>10000)
640		476.2101	476.2114		324.5		10.4	

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
641					134.7		5.0	
642		528.1799	528.1771		2889.0		36.9	
643	 4-[(4-{3-[(1-adamantylcarbonyl)amino]propoxy}phenyl)sulfonyl]-1-cyclopropyl-N-hydroxypiperidine-4-carboxamide hydrochloride	560.2794	560.2793		1134.1		11.4	

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
644	 4-[(4-{3-[(1-adamantylcarbonyl)(methyl)amino]propoxy}phenyl)sulfonyl]-1-cyclopropyl-N-hydroxypiperidine-4-carboxamide hydrochloride	574.2951	574.2943		2633.4		20.9	
645	 4-[(4-{3-[(2-adamantylamino)sulfonyl]propoxy}phenyl)sulfonyl]-N-hydroxytetrahydro-2H-pyran-4-carboxamide	557	557	9283	22.9	1726	4.3	>10000
646				(>10000)	(288.84)	(76.21)	(0.16)	(4296.95)

* * * * * * * * *

[1115] The above detailed description of preferred embodiments is intended only to acquaint others skilled in the art with the invention, its principles, and its practical application so that others skilled in the art may adapt and apply the invention in its numerous forms, as they may be best suited to the requirements of a particular use. This invention, therefore, is not limited to the above embodiments, and may be variously modified.